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PSYCHOLOGIC FACTORS IN LOW-BACK PAIN*

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IT is well known that the diagnosis of back pain is difficult and that the results of treatment, particularly in industrial practice, are not entirely satisfactory. Among the reasons commonly given for these diagnostic and therapeutic failures is the presence of psychogenic factors. The phrases "functional overlay" and "neurotic symptoms" are frequently and loosely used, on the basis of clinical impressions rather than carefully evaluated observations.

A few psychiatric studies of such patients have been presented,[1-5] and some of the clinical characteristics have been described. The present study was undertaken in the hope that we could cast further light on this problem, by using both orthopedic and psychiatric methods. Our purpose was twofold: to learn if there were features diagnostic of psychologic complications that could be observed without specific psychiatric technics; and to elucidate the nature of the psychologic problems involved in the hope of improving the treatment of these difficult cases. We are presenting here material and preliminary conclusions pertaining to the first of these aims only, on the basis of observation of a group of patients studied at the Massachusetts General Hospital.

METHODS

Thirty-six patients were interviewed and examined. Although no attempt was made to select patients most of them (29 out of 36) had had symptoms for three months or more. Some, but not all, were referred for study because they were considered by their physicians to have psychoneurotic problems. Twenty-three were industrial-accident cases and were receiving compensation.

The orthopedic work-up comprised a detailed history, physical examination, x-ray study of the lumbar spine and other special procedures such as myelography. The psychiatric investigation consisted of two or more psychiatric interviews, which were recorded and transcribed for subsequent analysis. The first interview was devoted to administering a "standard questionnaire," designed to obtain, in addition to a routine present, past and family history, a detailed description of the injury, the symptoms and the patient's reaction to his symptoms and treatment, and to elicit any neurotic symptoms and traits that might be present. This was not a routine question-and-answer interview between the patient and doctor. On the contrary the examiner attempted to get the patient to talk freely and spontaneously in various areas of interest, and the questionnaire was used as a guide to ensure completeness of material and for comparison of data on the patients seen. Subsequent periods were devoted to less formalized psychiatric interviews designed to elicit information pertinent to personality structure and interpersonal relations.

A psychiatric opinion regarding each patient was based on the following points: the nature of the symptoms and disability; past and present neurotic symptomatology; family and early childhood history; the nature of the patient's relations (marriage, job, parents and so forth); the nature of the lesion as determined by physical examination and other methods of investigation; behavior of the patient during interviews and on the ward during his hospital stay; and the nature of the patient's reaction to his illness and his associations and fantasies about it. This opinion indicated whether, on the basis of these criteria, the patient had psychologic factors significantly complicating his condition.

RESULTS

On the basis of the psychiatric evaluation described above psychologic factors were regarded as significant

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in the disability of 24 of the 36 patients. Of the 23 patients receiving compensation for injuries 14 were considered to show psychoneurotic complications.

Orthopedic Evaluation

In the orthopedic evaluation the criteria for the presence of a local lesion were unequivocal physical signs, positive x-ray and myelographic findings and positive operative findings. By these criteria 20 patients were considered to have some demonstrable structural cause for the pain, and 14 to have none; in 2 previous surgery obscured the picture at the time of observation. There was, however, no obvious correlation with the psychiatric findings, for of the 24 patients with definite psychologic complications, 12 were classified as having significant local lesions.

The pathological findings were as follows:

Typical disk protrusions or ruptures at the fourth to the fifth lumbar or at the fifth lumbar to the first sacral segment (8 patients).

Massive protrusion at the second to the third lumbar segment, not diagnosed preoperatively because it was obscured by associated arachnoiditis (1 patient).

Severe postoperative perineural fibrosis (2 patients).

Chronic arachnoiditis (1 patient).

Osteoporosis and compression fracture (1 patient).

Cauda-equina tumor previously treated by surgery and x-ray therapy (1 patient).

Scoliosis and severe degenerative changes in the lumbosacral spine associated with paralysis and shortening of one leg from poliomyelitis (2 patients).

Congenital deformity of the spinal canal, with undeniable evidence of root pressure at operation (1 patient).

Pseudarthrosis after spinal fusion (4 patients).

Spondylolisthesis (2 patients).

Old compression fracture of the second lumbar vertebra, with postoperative upper lumbar spinal fusion, pseudarthrosis and lumbosacral instability (1 patient).

Four patients had two lesions. Of these, 2 had a pseudarthrosis in an old fusion area combined with other lesions at the same level. One had perineural fibrosis after fusion for spondylolisthesis, and 1 had lumbosacral instability in addition to a pseudarthrosis in a fusion at another level. In the 14 patients in whom a definite local lesion was assumed to be lacking, all studies (physical, x-ray and operative) were inconclusive.

Psychiatric Evaluation of Histories

In the psychiatric evaluation of the entire group several striking characteristics appeared repeatedly in a number of patients:

The first consisted of a history of the present illness that was vague because of confused chronology and the introduction of material that seemed to have nothing to do with the injury and symptoms.

The second was an expression of either open or veiled resentment toward and criticism of the doctors and ancillary personnel because of alleged mismanagement and neglect.

The third comprised dramatic descriptions of the symptoms and of the patient's reactions to them.

The fourth was difficulty in localization and description of pain and other symptoms (this resulted from inability to localize the pain, a nonanatomic site and radiation of pain, an overly elaborate and overly minute description of symptoms or a complaint of pain in many areas obscuring a pain that might originally have had an anatomically consistent locus).

The fifth consisted of failure of the usual forms of treatment to give significant relief from pain.

The sixth included accompanying neurotic symptoms.

Clinical Examples

These characteristics can be best exemplified by verbatim extracts from the recorded psychiatric interviews.

In the first group the typical patient, when asked to describe the symptoms, replied as follows:

> Well, before the operation, I mean, I used to get these acute pains into my left leg, and I used to be sheeted [*sic*] in pain during this time; and, well, it got so that I'd have to be in bed for about six weeks at a time, that's after a period of 3 or 4 years. After that, before they came on, they wouldn't last as long as before the time—well, I thought it was sciatica and so forth, but each attack was getting worse and I went to the doctor, and the doctors thought I had pressure, and they didn't know what it was. Of course, I wasn't seeing the right doctor; he thought I needed a hysterectomy and so forth, so one doctor, he said, let's wait about six months to see how I felt. Well, about three months after that I was getting another attack and I came into his office and he told me I was so bad he'd like to do an emergency, anyway, and see what was causing it. So he took me in and gave me an emergency, and he did one of those sympathectomies on the pelvis to relieve the pressure and I don't know whether in the exploratory he tied my tubes and so forth. And after I went home I got the same attacks. So finally this doctor did suspect a ruptured disk, but he told me to call—he was an orthopedic doctor and he told me to call him when I had acute pain, and he came to my house and he said it was definitely a ruptured disk. I couldn't move at all, I couldn't even go to the bathroom, and he told me when I felt better to come back to him. So when I went back to him he said he couldn't do too much about it; he didn't want to operate. So I was getting to feel I was no good to the children; I was no good to anyone, not even to myself, lying in bed that length of time.

Another patient in this group when asked why he was in the hospital, gave the following reply:

> Oh, as soon as this last operation on my hip, the whole affair seemed to be recurring. When they took off the cast the left knee swelled up and I had water on the knee. The doctor thought it was a cartilage and put me in to operate

about the first of March, but as it happened I was starting to get pain just above here, and sharp shooting pains through the top of the knee which I had when I originally first entered. But after the operation on the back, it had seemed to clear up, but since the operation on the hip this condition of water on the knee seemed to — everything seemed to recur. See, like I get very bad pains. Like walking here I had to stop coming down on account of that knee is bothering me, and almost every morning when I wake up, I have pains in the back of my legs. This knee, I can't seem to bend it at all, but this knee I seem to get more bend in and when I went home from that operation on the hip, I tried to take this brace off. I thought if I could try, with the hip better, I thought — I mean, I figured that I'd try to keep my back straight without the brace if I could. It seemed, though, after a day or so of doing that, every time I got out of a chair my back would seem to drop. Well, I mean you're getting up on a slab like, and if I made a sudden move it felt like that back would drop; right around the operation the back would drop. I had severe pains there.

When asked what sort of treatment he had received, the typical resentful patient in the second group answered as follows:

I told you, they gave me steam baths — a little steam bath. Then they gave me — they put me in traction which I think was the worst thing they could have done to me. . . . Well, that set me back the whole way. Yes sir, — here's this leg that I can't touch, and they're pulling it from the hip yet. I'm all tightened and they put a ten pound weight on it. I kept telling the doctor to take it off. . . . Dr. C. is a terrific doctor, but I would say that hospital over there has got a lot to learn. They don't know how to take care of patients over there. The only thing I could say about over there is they told me I was the worst patient they ever had — that I messed up all their beds on purpose so the nurses would get mad at me . . . that upset me, but when I was going home, I guess they wanted to smooth it over and they said, "You were the next to worst patient," and I said, "Now you won't even give me credit for being the worst patient."

As an example of veiled hostility in the same group, a patient made the following reply when asked how she felt about being transferred from one doctor to another:

Oh, I liked it very much — I didn't have too much — I liked Dr. C., I mean he was good and everything. He tried to help me out in his way, but I can't explain myself. He just didn't — he wouldn't sit down and explain things to you. That's what I'm trying to say. Dr. M. would, I mean, if you asked him something he will come out and explain it to you — if it takes a half hour to explain it to you he will. Where Dr. C. kind of puts it in a kidding way and not really explain it to you. I really enjoyed having Dr. M. examine me and talk to me. I felt much better mentally, I mean, I felt all right. Toward the end there he tried to — he didn't mean it, I don't think — the way he said I was a little psychosomatic. That naturally makes you feel a little inferior.

Drama in an extreme form characterized the following description of his symptoms given by a typical patient in the third group:

[My wife] didn't know what to do with me, the pain was so severe. I jumped into the bathtub, filled it up with hot water, jumped out, lay down, bent down on my knees, stood on my buttocks, just to get heat, then I would take hot turkish towels and wrap them around me. Then I put my belt on, threw my belt off. Then I would pull my pajamas on; I ripped my clothes, my clothes were ripped to shreds from pain. Finally, I couldn't stand it anymore; I was going out of my mind.

Dr. What is the pain like?

What is it like? I couldn't explain that pain, doctor, because when I get it I just don't remember nothing. I just go out of my mind. When it gets so severe, I just go out of my mind. I don't know who is in front of me, what's in front of me. All I know, the next thing I am stark naked, running around the house, putting water in the bathtub, grabbing a bottle of alcohol, throwing it around and over me — I do the damndest things you ever heard of. You'd think a man was out of his mind.

In the fourth group vagueness of description and poor localization of pain characterize the reply of a patient to a request for information about the exact location (drama in the presentation of the complaints is also evident):

Like I say, I first noticed it in my knee; that's where the shooting pain starts. I used to get it in the left buttock, and, of course not so much the shooting pain in the back — I didn't have that so much. Real pain, like, a consistent, steady pain — and like when it first started, I get those shooting pains across both knees, and on the left, on the inside, right across the top. And in my right foot — that's another thing I can't understand. That main cord at the — right at the ankle; in the left one I didn't, but in the right one I did, and — I don't know, I usually get excruciating pain. Feels like that cord was being cut — terrific. I used to — err — yell "OW!" before I even stopped to think where the pain was. And I also got sharp pains in the back of these cords, in the back. I told you about that before. . . . I also got some pain in the joints, right in the crotch. It seemed to catch like . . . very sharp, on the left inside there. That would seem to — to be the one my whole hip got — that would seem to pinch something on the inside of the crotch — terrific pain. Since then, I mean, besides the leg and hip, the hip seems to click, the bones seem to click a bit — but since then just above the operation on the right side — although I've had it on the left side — it seems that in these columns every so often if I should get tired, it would seem almost as if a little crab would grab one of these, especially on the right.

In the fifth group a carefully taken and detailed history often elicited information that pain was constant and that such routine treatments as heat, rest, medication and tractions gave no relief. There might be fluctuation in the severity of the pain, particularly after medication had been given, but patients complained that nothing took the pain away completely. This characteristic was particularly applicable to patients in whom significant lesions were not found or in whom pain continued after surgical removal of a lesion with or without fusion. It appeared less significant in patients with untreated rupture of disks or tumors, which may cause constant pain.

Accompanying neurotic symptoms in this series most commonly included acute and chronic anxiety, insomnia, irritability, pressure-like headaches, depression with crying spells and chronic fatigue. An acute anxiety attack is a dramatic and frightening experience for the patient. He is seized without apparent cause by tachycardia and palpitations, frequently with sharp precordial pains, and a feeling that he cannot get enough air into his lungs and may smother. Trembling, sweating and chilly sensations may accompany this, as well as lightheadedness, faintness and fear that "something horrible is going to happen" (death or insanity), at times reaching the intensity of panic. More frequently, patients complain of chronic anxiety, which is less intense than an acute anxiety attack. There is a constant sensation of uneasiness and

tenseness, restlessness and vague apprehension, to which the patient often applies the word "tension" or "nervousness," that is not readily separated from feelings of irritability; patients jump at slight noises, are annoyed by the inevitable commotion caused by their children or find themselves losing their temper and lashing out physically or verbally in situations that have previously been handled calmly. Insomnia is not usually complete; patients often complain of waking up with a start frequently during the night, or they may awake early in the morning and be unable to get back to sleep. Another variation of the pattern is an inability to drop off to sleep until several hours have passed — hours spent in worry and rumination about their difficulties. The headaches are most commonly located in the occiput or vertex, are constant, may last days at a time and are described as a feeling of tightness, pressure or "fuzziness" in the head, rather than true pain. The depressive feelings are usually not severe, and only 1 patient in this group had serious suicidal ideas. Patients usually complain of feeling discouraged and of having lost interest in the things about which they were previously enthusiastic; they are easily moved to tears by minor irritations or frustrations. Finally, closely connected with feelings of depression is the complaint of being "tired all the time"; work, mental and physical, is an effort, and no relief is obtained from increased periods of rest.

Correlations

Of the total group of 36 patients 22 had 4 or more of these six characteristics, 11 had two or less and 3 had three. Table 1 shows how patients were classified by complete psychiatric evaluation regarding the presence or absence of complicating psychologic factors. It appears that there is good correlation between the findings by complete psychiatric evaluation and the presence or absence of these characteristics (the validity of the correlation is discussed below). Table 1 further divides the patients into those who were receiving compensation for injuries and those who were not. In this small series there was no obvious difference between the two groups.

Behavior of Patients

As a result of examination of the patients certain physical findings are considered suggestive of psychogenic elements in the clinical picture. Although well known for the most part they are re-emphasized here.

Facial expression and behavior indicating tension, anxiety, veiled or even outright hostility, severe depression or even excessive cheerfulness in the face of adversity.

Hyper-reaction to painful stimuli characterized by groans, grunts, wincing and excessive withdrawal when tender areas are palpated.

Abnormal postures not characteristic of low-back lesions.

Peculiar gaits suggesting hysteria. These were seen in 3 cases and, of course, were usually obvious. Inability to walk on tiptoe or on the heels, with exaggerated difficulty when this maneuver was attempted, was also observed and seemed to be characteristic.

Excessive limitation of all back motions, suggesting unwillingness to bend rather than actual limitation of motion from pain or involuntary muscle spasm. Comparison of forward bending in the standing position with that when the patient was sitting on the table with the knees fully extended often revealed a great discrepancy in the degree of bend between these two positions. As might have been expected much information about the true range of back motion was obtained by observation while the patient was dressing and undressing.

Diffuse and poorly localized tenderness. The location in some cases varied markedly when it was rechecked, especially if the patient's attention was diverted.

Disturbances of sensation not conforming to any dermatome pattern. Frequently, this was found to be a more or less complete hemihypesthesia if sensation was tested on the trunk as well as on the lower extremities.

Difference in limitation of straight-leg raising performed first in the supine position and then in the sitting position by extension of the knees. Inability or unwillingness to relax even when this test was performed slowly and gently appeared to be a manifestation of the tension or hostility characteristic of these patients.

TABLE 1. *Classification of Patients according to Presence or Absence of Complicating Factors.*

No. of Characteristics	Patients with Complicating Psychologic Factors	Patients without Complicating Psychologic Factors
Whole group:		
4 or more	21	1
3	2	1
2 or less	1	10
Totals	24	12
Patients receiving compensation:		
4 or more	12	1
3	1	0
2 or less	1	8
Totals	14	9
Patients not receiving compensation:		
4 or more	9	0
3	1	1
2 or less	0	2
Totals	10	3

Muscle weakness of the "jack-knife" variety. True weakness was hard to evaluate in patients presenting psychologic disturbances. However, in some cases muscles first exhibited good strength only to give way suddenly like a closing jack knife. Such weakness is, of course, not due to true paresis. The actual nature of a hysterical paralysis found in a patient with spondylolisthesis was at first not recognized by the examiner.

Discussion

"Complicating Psychologic Factors"

We have throughout referred constantly to "complicating psychologic factors" and have made no attempt to divide the patients according to the usual diagnostic classifications (hysteria, anxiety neurosis, compensation neurosis and so forth). We have done this for several reasons.

In the first place our interest has been in devising criteria to indicate that psychogenic factors are playing a part in symptom production or disability, or both, no matter what the clinical psychiatric label might be.

The various diagnostic labels, when derived primarily from the nature of the symptoms and the clinical course of the illness, are not particularly helpful either for judging the severity of the illness or for prognosis. To make an adequate decision about either of these, it is necessary to have adequate information about the patient's personality structure before and during the recent illness.

We wish to avoid furthering the common clinical diagnostic practice of attempting to decide whether a patient has "organic" or "functional" disease — that is, whether a symptom results entirely from a lesion or is entirely from psychogenic causes. In 12 patients considered to fall in the psychiatric group a lesion demonstrated by physical examination, by special studies or by surgery was considered of sufficient severity to cause symptoms. In these patients the final clinical picture was from both somatogenic and psychogenic causes.

Physical Examination

It should further be noted that in the psychiatric group routine orthopedic and neurosurgical examination alone frequently resulted in doubt and uncertainty regarding the diagnosis. This uncertainty arose from three sources:

Although some characteristic objective findings were present these were so obscured by other inconsistent or unexplained symptoms and signs that the examiner could not determine with certainty whether the suspected lesion was responsible for the clinical picture.

The lesion eventually found was unusual and therefore caused atypical signs and symptoms. These, coupled with coexisting neurotic symptomatology, made evaluation difficult.

Multiple operations and complications of previous surgery had produced sequelae that confused the picture at the time of examination.

Confusion in the mind of the physician at the end of orthopedic and neurologic examination should suggest the possibility of complicating psychologic factors. Although the physical findings are often emphasized in the evaluation of these patients, it should be stressed that such findings alone are frequently of secondary importance; their absence does not prove that symptoms are psychogenic, and positive evidence of complicating psychologic factors must be sought for in the history and behavior of the patient under observation. This evidence is supplied by the presence of the six characteristics described and exemplified above. Again, it should be emphasized that the final picture is frequently a result of both psychogenic and somatogenic causes, and positive physical findings cannot be ignored simply because the patient appears also to be suffering from a psychologic disturbance.

Six Characteristics in Relation to Complicating Psychologic Factors

The inference to be drawn from our study is this: in a patient showing four or more of the characteristics noted above, psychologic factors are an important part of the illness; in a patient with two or fewer characteristics, psychologic factors are not important. Because of the small number of patients in our series these statements are to be considered as tentative, and we believe that the first statement is more often valid than the second.

In a brief psychiatric evaluation one can with more assurance say that a patient has neurotic problems than that he has not. A positive psychiatric diagnosis is readily made on a basis of patients' statements about disturbing feelings and fantasies, symptoms and difficulties in personal relations. If a patient says that he has no disturbances in these areas he may be giving an accurate picture of himself, or he may be distorting the picture and consciously or unconsciously withholding information essential to an opinion about his psychologic structure and health. In our psychiatric evaluation of this group of patients, therefore, we were confident that certain patients showed important positive psychologic complicating factors, but less confident about a number of patients classified as having no psychiatric difficulties.

The six characteristics are easily observed by the examiner during his initial contacts with the patient, and the presence of four or more is strong evidence that psychologic factors are complicating the orthopedic disorder. It is not equally safe to infer an absence of complicating psychologic factors when these characteristics are not observable during the examination. The importance of the characteristics is that they provide positive criteria for detecting patients

with emotional disorders. Their absence is no guarantee that emotional disorders are not significant in any given patient, and we know at present of no way of making a rapid evaluation of patients in this group with suspected but not conclusively proved emotional difficulties.

Management

The treatment of patients with back pain, especially when injury and compensation are important factors, is notoriously difficult. From our experience with this group of patients we have formed certain tentative impressions about their management.

Patients with evidence of psychologic complications by the criteria described above should be referred when possible for psychiatric evaluation. Only on the basis of an understanding of the various facets of the patient's personality structure, environmental circumstances and interpersonal relations can a program of psychotherapy and an opinion about prognosis be made.

When psychologic factors are suspected surgery should be avoided if possible. This is particularly true of exploratory procedures without good indications from physical findings. Operations on this group of patients seem to complicate the clinical picture and to increase the psychologic disturbance without significantly improving the symptoms.

Compensation contingent on a continuation of symptoms increases the difficulty of making the patient symptom free. The solution probably lies in changing existing industrial-accident laws and policies.

A carefully planned course of psychotherapy should be an integral part of any rehabilitation program for patients with psychologic complications.

A better understanding of the indicated type and value of psychotherapy must await further study of the psychologic structure of the patient's illness and problems, and of the results of therapy.

Summary and Conclusions

From observation of a group of patients with low-back pain we have derived criteria revolving about the patients' attitudes toward their symptoms and treatment and their reaction to illness that are indicators of the presence of complicating psychologic factors. These criteria are based on the following six characteristics, which are readily observable if the patient is encouraged to discuss his condition: a history of the present illness that is vague because of confused chronology and because of the introduction of material apparently having nothing to do with the injury and symptoms; expression of either open or veiled resentment to and criticism of the doctors and ancillary personnel because of alleged mismanagement or neglect; dramatic descriptions of the symptoms and of the patient's reactions to them; difficulty in localization and description of pain and other symptoms; failure of the usual forms of treatment to give significant relief from pain; and accompanying neurotic symptoms.

The presence of four or more of these characteristics is good evidence that psychologic factors are complicating the illness. The presence of less than three suggests but does not necessarily imply an absence of such factors.

Almost half the patients with evidence of psychologic complications also gave evidence of lesions of the low back. This emphasizes that one must not think of the patient's illness in terms of either psychiatric or orthopedic disease. Both factors are frequently combined and intertwined to produce the final clinical picture.

The management of patients with psychologic complications should include, as part of the total rehabilitation program, psychotherapy based on the recognition of the presence and nature of the psychologic factors involved.

We are indebted to Dr. Stanley Cobb for his helpful suggestions and comments during the course of this study.

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STUDIES AND DIAGNOSTIC TESTS OF SALIVARY-GLAND AND THYROID-GLAND FUNCTION WITH RADIOIODINE*

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RADIOIODINE (I^{131}) has been used extensively in the diagnosis of thyroid disorders, and many tests have been developed.[1-3] Most of these tests are based on two aspects of thyroid activity: the removal of iodine from the plasma and the synthesis and secretion of thyroxin.

In clinical work on thyroid function in this laboratory both aspects of thyroid activity have been tested,[4] the first by a thyroid pickup measurement, and the second by a measure of the fraction of radioiodine in the blood plasma that is protein bound, both tests being taken twenty-four hours after the administration of the dose. The latter measurement, first described by Clark and Sheline,[2] is called the "conversion ratio."

Our investigations on over 1000 patients indicate that the pickup test is less reliable than the conversion-ratio test in the diagnosis of hyperthyroidism.[4] This result confirms the observations of other workers. Clark[5] has found the conversion-ratio method to be about 95 per cent accurate, as compared with an accuracy of 85 per cent for the pickup test. However, both tests seem disappointing in the diagnosis of hypothyroidism. It is obvious that these procedures and slight variations of them do not give the full story of thyroid function. Recently, Jefferies et al.,[6] recognizing the need for a better test for obscure hypothyroidism, investigated the effect of the thyroid-stimulating hormone (T.S.H.) on the radioiodine pickup test of euthyroid, hyperthyroid and hypothyroid patients. It was found that the pickup did not increase for hypothyroid patients after a dose of T.S.H. as it did for the others. Indications are that this test may be used in the diagnosis of hypothyroidism.

Recent work on the biochemistry of the thyroid gland indicates that other factors may have a bearing on the thyroxin level in the blood. Leblond and Grad,[7] Arvy, Debray and Gabe[8] and Bader and Kirkwood[9] have shown that the submaxillary salivary gland atrophies in rats that are thyroidectomized, fed thiourea or treated with thiouracil. In each case atrophy of the gland could be prevented by the administration of sufficient quantities of thyroxin each day. Also, the ability of the salivary glands to concentrate iodide ion is well known.[10-12] Finally, Fawcett and Kirkwood[13] have identified an enzyme tyrosine iodinase, responsible for the iodination of tyrosine to monoiodotyrosine in the thyroid gland. Assays for the presence of this enzyme[14] in a number of tissues in rats have shown that the submaxillary gland is consistently about twice as active as the thyroid gland of the same animal and that, with the possible exception of the kidney and stomach, none of the tissues except the salivary glands (submaxillary and parotid) and the thyroid gland show any activity.

These results indicate a definite relation between thyroid and submaxillary function and suggest that radioiodine tests on saliva of euthyroid, hyperthyroid and hypothyroid patients may correlate with and supplement conventional thyroid tests. With this in mind 76 patients — 36 euthyroid, 20 hyperthyroid and 20 hypothyroid — have been investigated.

The results show a remarkable correlation between the radioiodine secreted by the salivary glands twenty-four hours after the administration of a dose and thyroid function and give clinical support to the theory of Fawcett and Kirkwood[13] that the submaxillary salivary gland is concerned with the deiodination of thyroxin in the body. Details of these experiments are reported below.

During the preparation of this manuscript a paper appeared by Freinkel and Ingbar[15] dealing with the salivary-gland secretions of radioiodine in the first hundred and twenty minutes after the intravenous injection of radioiodine as iodide ion. They found no correlation between thirty-minute saliva-plasma activity ratios and thyroid function. Their short-time experiments, however, would only involve the ability of the salivary glands to concentrate iodide ion, which probably explains the apparent discrepancy between their results and the results presented in this paper.

EXPERIMENTAL OBSERVATIONS

I^{131} Tests of Thyroid and Submaxillary Function

Details of the radioiodine pickup and conversion-ratio tests have previously been described.[3] The radioiodine pickup and conversion ratios were measured with specially designed scintillation counters twenty-four hours after the administration of a 50-microcurie dose of radioiodine. In the latter test the protein-bound fraction of a 3-cc. aliquot of blood plasma was precipitated with trichloracetic acid, washed free of serum, redissolved with sodium hydroxide and finally diluted to the original 3-cc. volume. The radioiodine activity of this 3-cc. sample was then compared with the activity of a 3-cc. aliquot of the original plasma, the ratio of activities being called the conversion ratio. The sample activities were measured wet in plastic dishes, mounted over a crystal detector well shielded by lead.

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Finally, 3-cc. aliquots of saliva obtained from the patients by simple expectoration twenty-four hours after the administration of tracer doses of radioiodine were measured into plastic dishes, and the activity determined as before. In a number of cases saliva samples obtained from patients at various intervals after the administration of a dose of radioiodine were investigated.

The samples were counted with a scintillation counter for five minutes. With this counting time the natural background of the counter—100 counts per minute (c.p.m.)—could be determined to 5 per cent. The saliva samples investigated had relatively high activities (100 to 30,000 c.p.m.), and could be obtained with considerable accuracy. The sample activities of plasma and protein-bound iodine (PBI) ranged from 25 to 1100 c.p.m. and from 5 to 1000 c.p.m. above background respectively. In the few cases in which the sample activities were less than a fifth of background the effect of counting errors on the test in question was considered. For example, the saliva (S) and PBI samples for 1 hypothyroid patient gave activities of 16,000 and 5 c.p.m. respectively. The latter value could have been in error by over 100 per cent, and the S-PBI ratio used as an index for thyroid function would have reflected this error. However, the S-PBI ratio (16,000/5) was so high that the PBI count could have been in error by several orders of magnitude without changing the diagnosis.

Since scintillation counters were used to count gamma rays from wet samples self-absorption problems were negligible. Furthermore, there was no evidence of radioiodine losses from the sample dishes even on long standing.

TABLE 1. *Twenty-four-Hour Radioiodine Tests of Salivary and Thyroid Function in Normal Subjects.**

Subject No.	Total Pickup %	Conversion Ratio %	Saliva Activity c.p.m./3 cc.	Saliva-Plasma Activity Ratio	Saliva-PBI Activity Ratio
19	28	11	1123	16.5	160
28	23	18	3726	30.8	170
65	18	17	2306	29.2	177
22	26	13	1601	22.5	178
34	31	23	4180	45.4	199
30	32	19	1990	38.3	199
20	35	16	1878	36.2	235
Averages	28	17	2393	31.2	188

*All tests made 24 hr. after administration of 50-microcurie dose of radioiodine as iodide ion.

TABLE 2. *Twenty-four-Hour Radioiodine Tests of Salivary and Thyroid Function in Patients with Diagnosis of Hyperthyroidism.**

Patient No.	Total Pickup %	Conversion Ratio %	Saliva Activity c.p.m./3 cc.	Saliva-Plasma Activity Ratio	Saliva-PBI Activity Ratio
39	79	92	269	0.22	0.25
16	78	89	191	0.44	0.49
54	—	92	217	0.85	0.65
11	83	77	173	0.84	1.0
78	84	82	167	1.0	1.2
82	80	91	296	1.3	1.4
45	93	91	380	2.1	2.3
12	82	95	511	2.6	2.7
60	91	83	125	2.7	3.2
9	62	81	83	2.8	3.4
1	74	94	300	3.4	3.6
2	61	86	242	3.1	3.6
7	80	69	479	3.6	5.2
73	64	100	282	8.5	5.5
32	64	79	936	10.9	13.6
24	63	85	1630	17.9	13.8
14	56	45	760	14.1	31.6
25	50	51	590	17.9	34.7
44	55	51	505	20.2	38.8
67	42	66	1883	26.9	40.0
Averages	76	80	493	7.1	10.4

*All tests made 24 hr. after administration of 50-microcurie dose of radioiodine as iodide ion.

RESULTS

The radioiodine pickup, conversion-ratio and saliva tests were made on over 80 patients. The results obtained for these different patients were divided as follows: normal subjects (Table 1); patients diagnosed as hyperthyroid (Table 2); patients diagnosed as hypothyroid (Table 3); and patients diagnosed as

having normal or questionable thyroid function (Table 4). In each case the diagnosis was based on radioiodine tests and clinical symptoms.* The second, third and fourth columns of the tables give the twenty-four hour radioiodine pickup, conversion-ratio and saliva tests respectively; the fifth and sixth columns ratio), respectively. In each table the patients are listed in order of magnitude of the S-PBI ratio given in the sixth column.

Four different saliva samples were obtained from a patient over a ten-minute interval to determine the reproducibility of the measurement of the I^{131} level

TABLE 3. *Twenty-four-Hour Radioiodine Tests of Salivary and Thyroid Function in Patients with Diagnosis of Hypothyroidism.**

PATIENT No.	TOTAL PICKUP %	CONVERSION RATIO %	SALIVA ACTIVITY c.p.m./3 cc.	SALIVA-PLASMA ACTIVITY RATIO	SALIVA-PBI ACTIVITY RATIO
8	6.0	8.5	6100	28.8	338
42	2.8	10.5	9000	38.6	386
47	5.5	10.0	10,000	45.3	416
13	19.0	16.0	8500	72.7	447
29	17.5	10.0	7000	46.1	466
17	11.2	15.5	16,700	76.9	491
70	3.8	14.0	19,000	80.5	560
69	6.8	12.3	12,000	70.6	571
41	22.0	10.0	8700	65.5	624
83	1.8	8.6	8660	57.4	666
80	7.0	8.0	12,000	53.8	670
5	—	12.0	19,000	90.0	695
6	7.8	3.2	17,050	45.8	895
59	3.3	8.0	11,100	71.6	923
36	25.4	5.2	4370	50.8	970
26	3.6	8.0	18,000	78.9	1000
37	2.3	11.0	15,200	73.3	1055
58	29.2	3.0	2670	41.2	1335
18	27.6	9.0	24,400	161.6	1873
40	20.4	2.5	16,000	80.4	3200
Averages	11.7	9.1	12,172	66.5	879

*All tests made 24 hr. after administration of 50-microcurie dose of radioiodine as iodide ion.

give the ratio of the saliva activity to plasma activity (S-P ratio) and the ratio of the saliva activity to activity of protein-bound iodine in the plasma (S-PBI in the salivary-gland secretions. The results given in Table 5 show variations of 16 per cent. This fluctuation in the measured activity of a series of samples is

TABLE 4. *Twenty-four-Hour Radioiodine Tests of Salivary and Thyroid Function in Patients with Questionable Thyroid Function.**

PATIENT No.	TOTAL PICKUP %	CONVERSION RATIO %	SALIVA ACTIVITY c.p.m./3 cc.	SALIVA-PLASMA ACTIVITY RATIO	SALIVA-PBI ACTIVITY RATIO
43	39	40	1140	20.7	52
61	57	58	3925	33.3	57
48	42	22	1050	13.5	62
66	23	24	1657	17.6	75
21	54	53	1475	46.1	87
57	38	35	1850	30.8	88
23	50	23	1057	28.0	115
50	50	26	2400	30.2	118
52	37	16	956	19.5	119
64	50	30	2350	39.2	130
4	43	21	2136	27.0	134
15	32	22	1900	29.8	136
10	41	22	2400	33.3	150
55	35	25	2710	37.6	159
38	22	20	4740	33.1	170
68	—	12	7200	21.9	180
35	11	14	3525	28.0	195
62	45	11	2140	26.4	237
33	26	15	4550	37.6	239
49	8	14	3460	34.9	247
45	31	21	7250	53.6	251
31	28	18	7900	32.4	272
Averages	36	24	3077	32.0	149

*All tests made 24 hr. after administration of 50-microcurie dose of radioiodine as iodide ion.

*All patients suspected on clinical grounds of having abnormal thyroid function were dealt with in an investigative manner according to standardised clinical and laboratory tests. These patients were referred to us by their family doctors and in many cases by surgical and medical consultants. Basal metabolic rate, blood cholesterol and resting pulse rate had all been determined. When seen at the clinic they were again carefully screened by the clinicians in our group. Although for academic purposes we might accept the laboratory isotope tests as a basis for classification therapy was not guided by these laboratory tests without clinical confirmation. We were impressed, however, with the number of patients who presented a very equivocal picture whose isotope tests definitely indicated thyroid disorder.

small compared to the factor of 20 found between the saliva activities for hyperthyroid and hypothyroid patients.

Saliva samples were also obtained from a selected number of patients at intervals after the administration of a tracer dose of radioiodine, and the activity of 3 cc. of saliva in c.p.m. was determined. The results

obtained for 1 hyperthyroid, 1 euthyroid and 1 hypothyroid patient are given in Figure 1 as a log activity-time plot. The radioiodine level is seen to rise steeply for all patients, reaching a maximum in about four hours. The six-hour tests show average activities of 5000, 30,000 and 90,000 for the hyperthyroid, euthyroid and hypothyroid patients respectively as compared to activities of 280, 2000 and 81,500 for the twenty-four hour tests, which differed slightly from the averages given at the bottom of the fourth column in Tables 1, 2 and 3.

The saliva activities twenty-four hours after the administration of radioiodine varied from 83 c.p.m. (3-cc. sample) for a hyperthyroid patient to 24,000 c.p.m. for a hypothyroid patient, the average values being 493, 2393 and 12,172 for the hyperthyroid, euthyroid and hypothyroid patients respectively (Tables 1, 2 and 3, fourth column). Hyperthyroid

TABLE 5. *Repeated Saliva Counts.**

TIME min.	AMOUNT cc.	SALIVA ACTIVITY c.p.m./3 cc.
3.0	3.0	2306
8.0	0.8	3240
9.0	0.8	2780
10.0	1.0	2160

*24-hr. tests.

patients therefore secrete considerably lower amounts of radioiodine than euthyroid patients, whereas those with hypothyroidism show a much higher secretion of radioiodine in the saliva. Although the values for twenty-four-hour saliva activity are well spread out for the different groups of patients and are themselves indicative of thyroid function, there is some overlapping of values between the groups. For example, 2 hyperthyroid and 2 hypothyroid patients have saliva counts in the normal range. This slight overlapping (about 10 per cent) is not surprising in view of the relatively rapid change that takes place in the radioiodine level with time both in the saliva and in the blood.

When the saliva activity is determined in relation to that in the blood plasma (S-P ratio) an equally good correlation with thyroid function is obtained. The twenty-four-hour S-P ratio given in the fifth column of the tables varies from 0.22 to 161, the average values being 7.1, 31.2 and 66.5 for the three groups. It is interesting that the radioiodine level in the saliva for normal subjects is on the average thirty-one times that in the blood plasma. This is in good agreement with S-P ratios found by Honour, Myant and Rowlands,[11] and by Vanderlaan and Vanderlaan.[12]

However, a much better correlation between saliva tests and thyroid function is obtained if the saliva activity is taken in relation to the PBI activity in the plasma. It is seen from the sixth column that the S-PBI ratio varies from 0.25 to 3200, the average for the three groups of patients—hyperthyroid, euthyroid and hypothyroid—being 10.4, 188 and 879. This ratio therefore gives the maximum spread in values and seems to be an excellent index of the state of the thyroid function. It takes into account both the secretion of radioiodine by the salivary glands and the secretion of radiothyroxin by the thyroid gland twenty-four hours after the administration of a dose. Since the two factors work in opposite directions—that is,

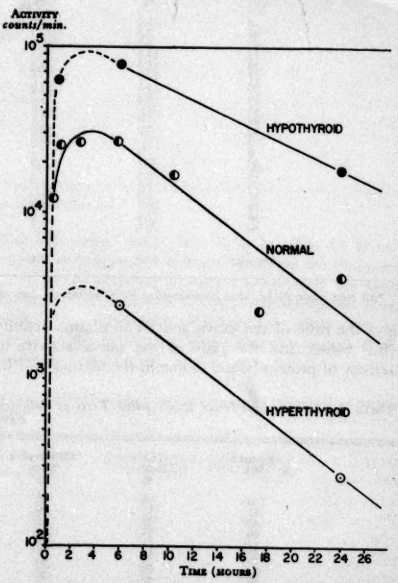

FIGURE 1. *Saliva Activity (3-cc. Sample) as a Function of Time after the Administration of 50 Microcuries of Radioiodine.*

saliva activity increases and PBI in plasma activity decreases with increasing hypothyroidism—the spread in the activity ratio for the hyperthyroid and hypothyroid patients is great.

The 22 patients listed in Table 4 were regarded as having normal or questionable thyroid function. The S-PBI ratio for these patients (sixth column) covered the range of values obtained for normal subjects (160 to 235) and extended on either side to the extreme hyperthyroid and hypothyroid ranges. Although the normal range will no doubt be extended as more patients are tested patients with S-PBI ratios between 50 and 100 are probably suffering from some disorder of the salivary-thyroid system and may be mildly hyperthyroid. Conventional radioiodine tests showed

only 2 of these patients (61 and 21) to be mildly hyperthyroid.

The results obtained by Freinkel and Ingbar[15] appear to be in direct contradiction to ours. According to their investigations there is no correlation between the magnitude of the S-P ratio and thyroid function as measured by the twenty-four-hour uptake of I^{131}. However, they measured the S-P ratio thirty minutes after the intravenous injection of radioiodine tracer as iodide ion as compared to our twenty-four-hour tests after oral administration. Their short-time tests probably concerned only the ability of the salivary glands to concentrate iodide ion. On the other hand the twenty-four-hour tests (S-P ratio) involved both iodide ion and organically bound iodine.

The plot of the saliva activity as a function of time after the administration of a tracer dose (Fig. 1) shows that with our procedure the maximum saliva activity is reached in about four hours and that at this time there is a marked spread between values for hyperthyroid and hypothyroid patients. The activity of the salivary-gland secretion rises steeply over the first hour, and sample activities measured during this period were quite erratic. Freinkel and Ingbar[15] report saliva activities as a function of time for 2 treated myxedematous patients only. Their results indicate a maximum saliva activity in about an hour after intravenous injection of tracer iodide ion. This earlier rise to a maximum is, of course, to be expected with intravenous injection.

It should also be pointed out that the counting procedures of Freinkel and Ingbar were different from ours. Whereas we used scintillation counters and measured the gamma activity of wet samples they measured the beta activity of dried samples with an end-window Geiger-counter tube. In the measurement of betas from dried samples self-absorption problems are paramount, and there is always the chance that iodine will be lost in the drying process. Freinkel and Ingbar did, however, make self-absorption corrections and added carrier iodine to their samples to reduce iodine losses to a minimum.

Discussion

Although the S-PBI ratio appears to be the most accurate radioiodine test for thyroid function saliva counts by themselves might be used as a rough diagnostic test with fair confidence (Tables 1-4). The results plotted in Figure 1 show a maximum activity in the saliva secretion at about four hours and indicate a large spread in values between hyperthyroid and hypothyroid patients.

Hypothyroidism

Pickup and conversion-ratio tests have not been satisfactory in the diagnosis of hypothyroidism. The results of Tables 1 and 3 show that for these tests there is a considerable overlapping of values between euthyroid and hypothyroid patients, and in many cases the pickup and conversion-ratio tests are conflicting. In the past it has been necessary to consider both tests together with the clinical symptoms to diagnose hypothyroidism, and cases of obscure hypothyroidism have no doubt escaped detection. The S-PBI ratio, on the other hand, provides an exceedingly reliable test for hypothyroidism. The patients regarded as hypothyroid all had ratios above 338 and an average of 879 as compared with a top value of 235 and an average of 188 for normal subjects. The saliva tests should therefore be particularly useful in the diagnosis of hypothyroidism.

Salivary-Thyroid Function

According to Fawcett and Kirkwood[14] the enzyme tyrosine iodinase responsible for the iodination of tyrosine in the thyroid gland is also present in equivalent concentrations in the submaxillary and parotid salivary glands. Since the enzyme will catalyze either the iodination of tyrosine or the degradation of monoiodotyrosine, depending on the redox potential of the tissue concerned, the authors suggest that the submaxillary and parotid glands may be responsible for the degradation of thyroxin in the body and the recycling of the iodine to the thyroid gland as iodide ion. They suggest further that conditions of hypothyroidism and hyperthyroidism may depend to some extent on salivary-gland as well as thyroid function. In this connection the S-PBI ratio test used in the present investigation involves both the secretion of radiothyroxin into the blood and the secretion of radioiodine by the salivary glands. The fact that this test appears to be much more accurate than conventional tests (thyroid pickup and so forth) in the diagnosis of hyperthyroidism and hypothyroidism is strong evidence that the salivary glands play a role in the body iodine cycle.

In connection with the S-PBI ratio it should be pointed out that the protein-bound iodine activity in the blood twenty-four hours after the administration of a tracer dose of radioiodine is not by itself an index of thyroid function. Twenty-four-hour pickup and conversion-ratio tests on over 1000 patients in our clinic showed little correlation between thyroid function and PBI activity. Patients with extreme hyperthyroidism often have a low PBI (in plasma) count comparable to that of euthyroid and hypothyroid subjects. On the other hand the S-PBI ratio, which takes into account the salivary-gland secretion of radioiodine as well, appears to be an excellent index of thyroid function. This is not merely the introduction of a factor proportional to the radioiodine level in the plasma and therefore another conversion-ratio test, for the saliva to plasma ratios are by no means constant, varying by more than a factor of 10 (Tables 1-3).

The excellent correlation between S-PBI ratios and

thyroid function indicates, therefore, a definite relation between thyroid and submaxillary function. The results show further that the submaxillary gland not only concentrates iodide ion[10-12] but also is concerned with thyroxin, perhaps, as suggested by Fawcett and Kirkwood,[14] in its deiodination.

Many diseases of the thyroid gland are referred to as either hyperthyroidism or hypothyroidism. It is consequently not surprising that a number of tests are required in the diagnosis of thyroid disorders. Not only is the pituitary gland involved but also it is now fairly certain that the salivary glands play a part in the iodine cycle through thyroxin. The saliva test can therefore be expected to provide additional information concerning thyroid-salivary function as well as an excellent diagnostic test.

We are indebted to Dr. W. Jackson, medical fellow, and to Dr. R. K. Wanless, Mr. Harold Amy, Mr. Edwin Taylor and Miss Mary Evel, who assisted in carrying out the many tests, and to the Ontario Cancer Treatment and Research Foundation and the Hamilton Medical Research Institute for financial assistance.

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URETERAL ECTOPIA IN THE FEMALE*

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BOSTON, MASSACHUSETTS, AND BANGOR, MAINE

A HISTORY of urinary incontinence since infancy, associated with otherwise normal micturition, suggests ureteral ectopia. The ectopic orifice is usually in the midline just posterior to the urethral orifice (Fig. 1). Less commonly it opens into the upper vagina, the cervix or the uterus. The orifice may be obscured by local inflammatory reaction, and its identification and catheterization require anesthesia. The ectopic ureter, which nearly always originates from a duplicated upper renal segment, is often dilated as the result of cicatricial stenosis of the exposed ureteral orifice. The tissue of the anomalous renal segment may be hypoplastic, or it may be damaged by chronic obstruction or infection (Fig. 2).

Intravenous pyelograms may show the duplicated renal segment (Fig. 3). Often, however, the function of the anomalous segment is so poor that there is no visible excretion of contrast medium or of indigocarmine, which may be injected intravenously to help locate the ectopic orifice. In such cases the soft-tissue outline of the nonfunctioning supernumerary segment may be seen (Fig. 4), or relatively incomplete pelvic and calyceal shadows may be present on the affected side (Fig. 5 and 6).

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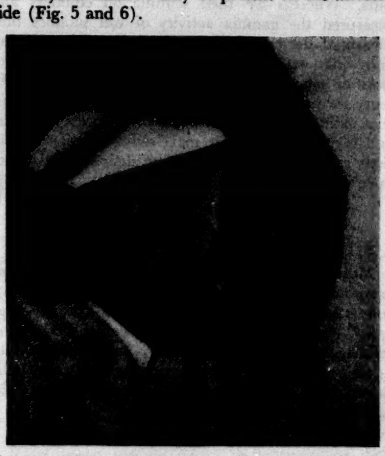

Figure 1. *Ectopic Ureteral Orifice in Case 1 (with Catheter Inserted).*

The type of operation required depends on the character of the vascular supply of the kidney and the

degree of damage existing in the duplicated, ectopically draining segment (Fig. 7). If the duplicated segment has a separate vascular supply but is too dilated to warrant preservation (Fig. 7*A*) heminephrectomy yields excellent results; when the vascular pedicle is not duplicated (Fig. 7*B*) segmental resection of anomalous renal tissue is necessary. Total ureterectomy may also be required, depending on the conditions encountered. If the ectopic ureter is not dilated and

FIGURE 2. *Operative Findings in Case 1.*
The dilated, anomalous renal segment is seen at the upper pole.

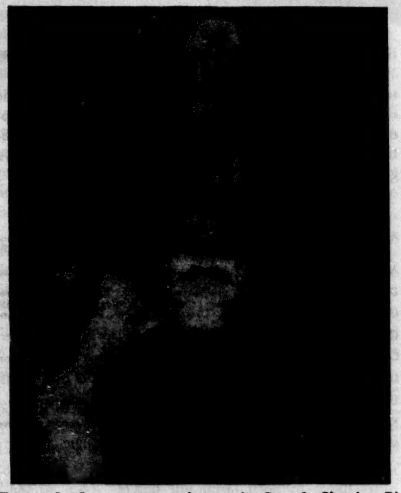

FIGURE 3. *Intravenous pyelogram in Case 1, Showing Bilateral Ureteral Duplication, with Tortuosity and Dilatation of the Lower Part of the Duplicated Left Ureter.*

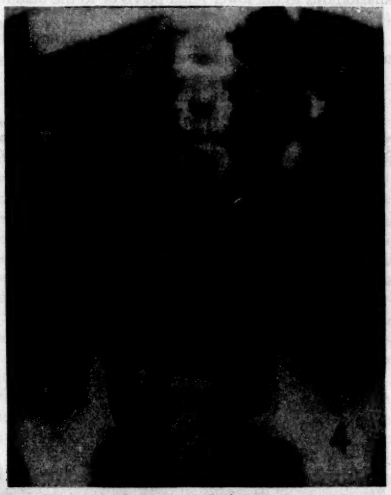

FIGURE 4. *Intravenous Pyelogram in Case 2.*
The shadow of the nonfunctioning duplicated segment at the upper pole of the left kidney is outlined by the dotted line.

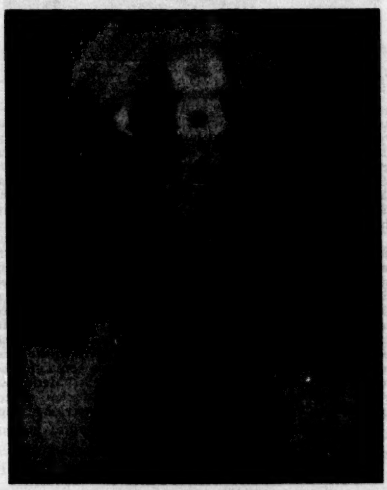

FIGURE 5. *Intravenous Pyelogram in Case 3, Showing an Incomplete Calyceal and Pelvic System on the Left.*

its contents are not infected it may be preserved by anastomosis to the lower renal pelvis or to the bladder (Fig. 7*C*).

To illustrate the varying problems of diagnosis and treatment the following cases are presented.

Case Reports

Case 1. H.P. (N.E.C.H. 77819), a 29-year-old married woman without children, had been incontinent of urine since infancy and had noted that she voided with 2 urinary

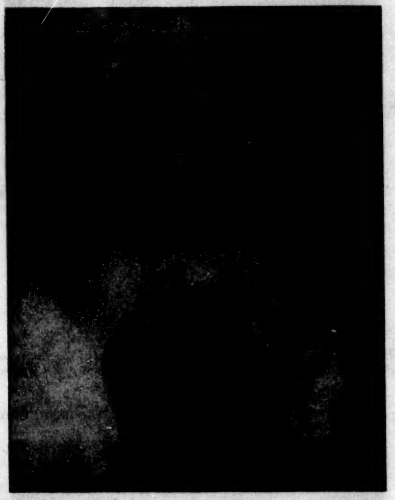

Figure 6. *Retrograde Studies in Case 3, Showing the Duplicated Ectopic Ureter.*

streams, 1 forceful and 1 weak, 1 cm. apart. An intravenous pyelogram (Fig. 3) showed bilateral duplication of kidneys and ureters and suggested a reservoir-like, dilated, tortuous ureteral segment in the left pelvis, which, after identification of the ectopic orifice (Fig. 1) under anesthesia, was catheterized. Heminephrectomy gave a good result. The anomalous renal tissue (Fig. 2), studied microscopically, showed cyst formation and scarring.

Case 2. L. J. (N. E. C. H. 69161), a 24-year-old married woman with a history of high-forceps extraction 2 years previously, was examined because of a recent attack of pyelonephritis on the left (a previous attack had occurred during pregnancy). She had been aware of a profuse vaginal discharge since childhood but had only recently suspected urinary incontinence. Pelvic examination disclosed a soft, tubular mass on the left that was consistent in structure and location with a dilated, ectopic ureter, and verified the presence of abundant, watery fluid in the vagina containing no pus but numerous desquamated epithelial cells. Meticulous search under a general anesthetic failed to disclose an ectopic orifice. The excretory urograms, however, had suggested a poorly functioning anomalous upper renal segment on the left (Fig. 4). At operation a strikingly dilated duplicated ureter and the attached renal segment were removed. The ureter was probed from above and the scarred and previously unrecognizable orifice found in a location similar to that seen in Case 1. The renal tissue, examined microscopically, proved to be rudimentary and to show chronic inflammatory reaction.

Case 3. E. G. (E. M. G. H. 79411), a 26-year-old nulliparous housewife, gave a lifelong history of constant leakage of urine but nevertheless emptied her bladder at normal intervals. Her family physician had noted a dimple within the vestibule posterior to the urethral orifice in the midline. Preliminary intravenous and retrograde pyelography revealed partial duplication of the upper urinary tract on the right and a comparatively small renal pelvis on the left (Fig. 5). Under anesthesia it was possible to catheterize the vaginal dimple, and the ectopic, dilated ureter was seen to originate from a single, hydronephrotic calyx (Fig. 6). A good result followed heminephrectomy. Microscopical examination of the specimen demonstrated a thinned, fibrotic ureteral wall and dysplastic renal tissue.

Conclusions

A history of urinary incontinence or abundant watery vaginal discharge since infancy suggests ureteral ectopia. Diagnosis is made by recognition of the ectopic orifice, if possible, and by pyelography. Operation (the type depending on variable local conditions) may be expected, if properly planned, to give good results.

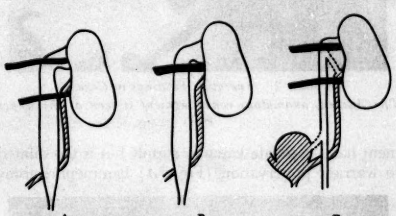

Figure 7. *Diagram of the Anatomic Situations That May Be Encountered at Operation.*

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SPECIAL ARTICLE

GENERAL MEDICINE*

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THERE are thousands of general physicians and millions of their patients who are more than happy with their mutual relations and ask for no other. Nevertheless, this field is one of the most controversial in medicine, and a volume would be required to present all phases of the many issues involved.

Even the name of the field and the title of its practitioners has been subjected to much discussion. "General practitioner," "family physician," "general physician," "local medical doctor," "personal physician" and "generalist" constitute a sample list attacked and defended by all branches of the profession. I have arbitrarily chosen the term "general medicine" to describe the field and "generalist" to identify the physician practicing it. The much more complicated and important aspects, such as the definition of a generalist, the advantage of adequate and specific hospital training, definite qualifications for practice and the role of this practitioner in the field of surgery are not so easily dealt with.

It is greatly to the advantage of some generalists, specialists, educators and laymen to leave the nature of general medicine undefined, to satisfy the fears, poses, prejudices, preconceptions and hopes of some members of these classes. It requires much less effort and fewer people are offended if these vital problems are not met head on. As long as the nature of general practice remains uncertain it will be impossible to reach a necessary agreement about the extent of the general physician's participation in certain specialized fields. It will be equally impossible to establish the exact level of diagnostic and therapeutic responsibility.

Is general medicine an anachronism when conducted at the highest level? There is statistical evidence that 75 per cent of pediatric care (in some places, 100 per cent) and 76 per cent of obstetric care (in some areas, 90 per cent) are the responsibility of the generalist. There are no statistics dealing with general surgery, internal medicine and a host of minor fields, but anyone familiar with rural, semirural and small-city medicine knows that the major portion of the work in all these areas at the community level is the responsibility of the generalist. The 1950 census revealed that 36.2 per cent of the population of this country lived in rural areas (towns of 2500 or less). When the population of small cities cared for by generalists is added it seems that at least 50 per cent of the people call upon the generalists for their care. There are studies that have revealed that well trained generalists with adequate hospital, laboratory and consultation services care for approximately 85 per cent of all conditions met in their communities. Granted that this does not present the whole picture, there appears to be enough statistical proof that there is a vital place in medical practice for general medicine.

Theoretically, general medicine is in an enviable position, but the disquieting truth remains that, heretofore, not more than 10 per cent to 20 per cent of generalists were judged to be competent according to the standards of excellent observers from their own field. This sad state of affairs has improved, but the situation is still not satisfactory.

What follows is an attempt to summarize the various patterns of general medicine and the quality of care it affords and to define a qualified generalist. Finally, an attempt is made to suggest certain programs of education and training and to indicate and analyze various locations that might be of interest to those who are considering entering this field.

PATTERNS OF GENERAL MEDICINE

Generalists may be placed in many classifications, but three basic types seem to develop immediately, or a few years after, hospital training. The first consists of those who have been inadequately trained by one year or less of "rotating" internships. The second includes those whose training has been more nearly adequate, consisting of two or more years of internship-residency programs. The third comprises generalist-specialists, a few of whom have been primarily trained, but most of whom gradually develop from the first two classifications. A few may eventually become qualified specialists. Owing to geographic considerations there are, in addition, five general patterns of practice: urban, suburban, small city, semirural and rural. Each, in turn, may be classed as satisfactory or unsatisfactory in terms of quality of medical care.

URBAN PRACTICE

In the densely populated area of large cities the inadequately trained generalist works in the midst of teaching hospitals and the best specialists available. He is not qualified for appointment to the staff of a recognized hospital, and his patients usually cannot afford private consultations. He works alone in his office, virtually isolated from those in his field and the excellent specialists who surround him, except so

*Adapted from the chapter of the same title in the forthcoming book, *The Physician, His Practice and His Business*, by permission of the publisher, Little, Brown and Company, Boston.

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far as he refers his patients to the teaching hospitals and clinics, where they are immediately lost to his view.

He depends on volume and low fees and develops a rapid "spot diagnostic" technic that allows him to see, but not to examine, a patient every five to fifteen minutes. He has no office assistants or laboratory facilities worthy of the name. The results of such a practice can be seen in the outpatient departments and wards of teaching hospitals, where the terms "general practitioner" and "L.M.D." forever identify the generalist in the eyes of students, house staff and educators as a physician of inferior status.

In this underprivileged medical environment is found an occasional physician whose training, conscience and decency will not permit him to follow this path, and he may become quite closely, although not formally, connected with one of the teaching hospitals. An able diagnostician and therapist who hovers on the borderline of financial defeat may be the result of excellent medical practice in this environment.

Physicians from Class 2 (those who are well trained) are seldom found here unless they are forced into the pattern. Class 3 generalists (generalist-specialists) have no real place in this group. An excellent economic cross-section of patients and good hospital affiliations are necessary to offer them survival.

Suburban Practice

As the thickly populated urban areas are left behind the suburbs furnish quite a different picture. Here the inadequately trained physician may receive an appointment to the staff of a good, small, local hospital on a trial basis. The more enlightened trustees of such a hospital will not allow him to perform major surgical procedures, but if he has a reasonably pleasing personality and is ambitious, conscientious and hard working, his worth may eventually be recognized. He has the opportunity of personally meeting the excellent consultants associated with the local hospital, some of whom may have homes in the suburban area. If the generalist in question is reasonably well endowed with some of the attributes listed above and if he is interested, postgraduate, educational programs will be devised for him. As he improves he will be recommended by the consultants and others to patients in all economic brackets in the area.

Lest this be considered a simple program, I should like to state categorically that it requires from three to five years of postgraduate study during practice to make up for the loss of one year of a residency program. It can be stated that the generalist with a year of internship training will require from six to ten years of conscientious postgraduate study for approximately one or two months each year to bring himself to the level he would have attained after a properly conducted two-year residency program in internal medicine.

While this physician is attempting to compensate for the deficiency of his training qualified specialists and better trained generalists may be gradually added to the suburban community, and his economic and professional survival may become a race against time.

The suburban area close to teaching centers with an excess of specialists, some of whom may have local offices, offers the keenest competition and calls for superior training for Class 2 generalists. This is one area that two years' preparation in internal medicine with added training in pediatrics and obstetrics allows for gradual evolution. With such a background and proximity to a teaching center the generalist can continue his medical education and qualify for certification by the American Board of Internal Medicine within ten years. This ability to effect a transition may become increasingly important in such an environment.

Class 3 generalists (generalist-specialists) have a diminishing role in the suburbs, where young, fully trained surgeons, anesthesiologists, orthopedists, obstetricians and pediatricians are immediately available and where a large number of medically intelligent middle-class and upper-class families often demand specialized attention in these and other fields because such services are easily obtained.

Small-City Practice

Although most of the conditions discussed above under suburban practice operate in a small city there are certain dissimilarities caused by increasing distance from medical centers and variation of medical development of the individual city. Some small urban areas may have a highly developed group of specialists working separately or as a clinic. Other cities, a few miles distant, may support only a qualified radiologist, a "visiting" pathologist and one or more otolaryngologists. Without a good internist, surgeon, anesthesiologist, pediatrician, obstetrician and so on in his area, the generalist may be forced to become increasingly familiar with some of these fields if he is separated by one or more hours from qualified specialists. Here, as in every other good environment, superior training enjoyed by Class 2 generalists is an advantage. In small city practice Class 3 generalists have responsibilities that depend entirely on how far the city has turned in the direction of specialism.

Semirural Practice

For the purposes of this chapter semirural practice indicates the type of work encountered in towns of approximately 3000 population, in addition to the surrounding towns, all served by one community hospital that furnishes care for a total population of 10,000 to 20,000. Here there is a similarity to small-city and suburban practice with one great difference — there are few, if any, local specialists. The population of this area may or may not be devoted to agriculture. In many Eastern areas large numbers of the original population have been displaced by a cos-

mopolitan population; they are financially solvent, medically intelligent and quite ready to accept the only type of physician immediately available, if he is a generalist with a good reputation.

The physician who attempts to care for this group must be a competent diagnostician in internal medicine, general surgery, obstetrics and pediatrics. His therapeutic range enables him to treat approximately 85 per cent of these patients at the level of a specialist, and he has a list of about a dozen specialists, located in the nearest medical center, with whom he works closely. These specialists are considered as much a part of his practice as the generalist himself.

Comparatively few of these men (perhaps 1 in 10) do major surgery. The office of such a physician is well organized, with a secretary, nurse and technician, or some combination thereof, and his community hospital has excellent basic facilities. There is often a visiting radiologist and pathologist who has charge of radiology and the clinical laboratory.

How does this physician obtain his training? If he is to take these not inconsiderable responsibilities directly after hospital training, it will be to his advantage (provided he does not intend to do major surgery) to have the equivalent of two years of internal medicine, during which he must have training in general surgical diagnoses through the emergency ward and outpatient department. He should have several months' additional experience in obstetrics and pediatrics — probably three to six months of each. If he has the responsibility for general surgery he should have three years of straight surgical training, followed by six months to a year of experience in general medicine, pediatrics and obstetrics.

Although a generalist, with such broad responsibilities, may be trained by postgraduate study after a year of rotating internship, the time required is approximately six to fifteen years, depending on his surgical responsibilities, his innate ability and the amount of time he can give to postgraduate study. He is accepted by the people and the specialists in the semirural situation because he is necessary to the first and noncompetitive to the second. He therefore develops all his potentialities without artificial restraints.

It is in this situation that many generalists become qualified or semiqualified in various specialties (Class 3). The specialization may take place in suburban and small-city areas when there are few specialists, but hospital restrictions and other factors militate against such a course except in the field of internal medicine. In the semirural environment there is real necessity for a surgeon who can take responsibility for the many obstetric complications and who is equipped to perform a creditable forceps delivery or cesarean section. There must be someone to perform emergency tracheotomies and operate on really acute abdominal conditions, in addition to caring for serious injuries at a certain level. Someone must be able to give endotracheal anesthesia, and routine and emergency electrocardiograms are a necessity. The generalists can carry out these assignments if they are well equipped by early hospital or continuous postgraduate study. No claim is made that they should undertake these procedures if better qualified men are available.

It must not be forgotten that the more interested the generalist becomes in a specialty, the less competent he may be as a generalist. The generalist-specialist has been emphasized in this semirural area because this is one environment in which he is almost indispensable. However, all classes of generalists can fit into these areas, where everyone is welcome to an understaffed territory. Many regions suffer chronically from lack of doctors, and conscientious practitioners of whatever training working together can practice remarkably good medicine. It is true that a few semirural regions have become highly specialized, but this is unusual and different from most patterns.

Rural Practice

Rural practice is arbitrarily described as a type so isolated that it is impossible for the physician to reach the nearest hospital once or twice a day without jeopardizing other elements of his work. Such a practice is usually widely spread for a distance of many miles in all directions, and it may require hours of motoring each day to care for patients. It is generally difficult to organize a successful office practice where reasonably accurate diagnoses can be made. Sometimes, this is because the physicians in this environment have made no attempt to educate their patients to come to them.

Of course, such a practice can be conducted at a high level, but the tendency seems to be for the generalist in these situations to deteriorate technically because he does not have the time for postgraduate study, there being no one with whom he can leave his practice. He does not have the daily contact with other physicians that is a constant source of postgraduate education. Furthermore, he does not take complete care of really ill patients, and in many cases this type of work resembles the highly unsatisfactory practice conducted by generalists in thickly settled urban areas. Physicians with Class 2 and 3 training might find their experience wasted in this particular environment, for obvious reasons.

Definition of a Generalist

Reference was made above to the lack of definition of general medicine. Because of this lack and the resulting ambiguities of status, limitations and responsibilities many young physicians are unwilling to take up what appears to be an outstandingly thankless form of medical practice. Such a situation gives rise to a vicious circle, harmful alike to the best interests of the medical profession and to the public.

It is quite possible to define what the qualified generalist must know and must do.

Outstanding points to be noted are as follows: at least 75 per cent of his work falls into the fields of major and minor medical and surgical diagnosis and major and minor medical treatment, with undetermined overlapping into the field of psychiatry; certain special fields are frequently omitted from general practice (this is important in terms of function and education of the general practitioner); certain special fields — principally psychiatry, dermatology, neurology, gynecology, orthopedics, otolaryngology and urology — cannot be omitted, being an essential part of all general practice.

Before details of the full implications of all this are considered, a concise and explicit definition of a general practitioner is necessary, in terms of function, not in the abstract terms often used in previous attempts at definition. A generalist is defined as a graduate in medicine from an approved medical school who, after specific hospital training, is capable of assuming responsibility for the following areas of medical care:

The diagnosis of all major and minor medical and surgical conditions (except extremely complicated and rare ones).

The treatment of the great majority of the medical conditions diagnosed (but only the really minor surgical conditions).

Obstetrics to the level of uncomplicated deliveries, the early recognition of abnormalities and the necessarily immediate treatment of the few unpredictable but potentially catastrophic emergencies that may arise.

Pediatrics to the level required for medical and surgical diagnosis and treatment.

Psychiatry to a level permitting the differentiation of serious, potentially serious and mild psychoses and psychoneuroses, and permitting the treatment of the last mentioned by intelligent support, clarification and reassurance.

This definition, within broad limits, is specific in terms of function and responsibility. However, like all definitions that attempt to encompass a wide and diffuse range of activities, events or phenomena, it requires considerable explanation and qualification, which have been given elsewhere.*

It may be said, however, that the separation of medical and surgical conditions, from a diagnostic standpoint, is arbitrary in the field of general medicine. The subfields have varying relations to the whole: functional conditions make up 30 per cent or more, of the problems. Neurology is very important because errors in this field, such as the inability to recognize early meningitis or subdural hematoma, may be fatal. Obstetrics carries certain clear and immediate responsibilities implicit in its definition. Gynecologic diagnosis is so important that the generalist must accept broad and definite responsibilities in this area. Dermatology, urology and otolaryngology have limited responsibilities. Public-health duties are tenuous and variable except when associated with school medicine and maternity and child-welfare services.

The technics of major surgery are not here considered as a responsibility of the generalist. Incision and drainage of abscesses and the placing of a few skin sutures is thought to be his technical commitment except for diagnostic procedures (sigmoidoscopic and pelvic examinations and so forth.)

Education, Hospital Training and Choice of Location

Teaching general practice in medical schools and teaching hospitals seems to be a process of bringing medical students into somewhat prolonged contact with excellent generalists who can demonstrate by precept their ability and the extent of the field of general medicine. Able generalists of this caliber are exceedingly hard to find. The teaching can best be accomplished in the offices and community hospitals of the generalists, although outpatient departments and domiciliary programs conducted by generalists are not to be ignored. The fourth-year student contemplating the field of general medicine is indeed fortunate if he has the opportunity of working with qualified generalists for a few weeks or months. Such a background and a definite idea of the specific community, or at least the type of community, desired allows the student to select hospital training suited for his future work. A two-year rotating internship, which is recommended by qualified generalists, is probably the safest choice. If it seems inadequate supplementary courses of three to six months can be considered. Two years of internal medicine, including some pediatrics and experience in the emergency ward, followed by three months of obstetrics prepares generalists for specialist competition and eventual certification by the American Board of Internal Medicine.

The day of learning basic major surgical technics in community hospitals is rapidly passing. If a medical student is firmly convinced that the community in which he is to practice requires a generalist-surgeon, he should prepare himself by three years of approved surgical residencies, adding six months to a year of medicine, obstetrics and pediatrics as indicated. Such protracted training will, of course, require more time than preparation for some of the specialties, and the practical consideration of economic and professional compensation immediately arises. Careful evaluation of the general-practice residencies of one to three years is necessary. Some of these programs are less than ideal, having been devised by excellent specialists who unfortunately have had no real experience in the field of general medicine.

One-year internships, on the other hand, can have real value if the intern drives himself day and night to obtain all possible experience. Unfortunately, many such programs are badly conceived, with "scut work" and "hospital services" predominating. Laborious,

*Collings, J. S., and Clark, D. M. Medical practice, today and tomorrow. *New Eng. J. Med.* 248:141-148 and 183-194, 1953.

protracted and expensive postgraduate studies can also compensate for lack of an adequate residency program.

Something should be said about preparation for group practice, regarding which there are two diametrically opposed points of view. One holds that a generalist has no place in a group of specialists, whereas opponents of this theory state that all patients should first be "screened" by generalists whether in private clinics or outpatient departments. Practically, it may not be simple to balance specialists and generalists in the same group, but this goal can be accomplished. One great advantage that a group can offer the young generalist of modest hospital training is gradual experience in close association with specialists and seasoned generalists.

An attempt to present the field of general medicine objectively must invariably result in a pessimistic note because generalists, specialists, medical educators and the public have given less constructive consideration to general medicine than to other fields. This lack of consideration and understanding has placed general medicine in an unenviable position, but there are many indications of an increasing interest during the last decade. Some of the adverse criticism of the present is a holdover from the past and is not entirely valid.

The well trained generalist can offer intimate personal service to which the patient can turn for assistance in time of all physical and mental distress and a sound, basic diagnostic and therapeutic service that will assure him a first line of protection against the common hazards of illness and injury. This service can be offered by no other type of doctor, and such an opportunity is an unusually satisfying experience for many physicians. Some of the advantages of this field are that it can be practiced in many areas where the specialist cannot survive; that generalists who are financially handicapped are usually able to depend on an immediate income whereas some specialists may be forced to wait several years before they can become self-supporting, and that in the rural and semirural areas especially, the excellent, experienced generalist commands a place in his community enjoyed by few other people in the world.

Conclusions

If these concepts are approximately correct it appears that the student who seriously considers entering this field should try to obtain several weeks or months of close association with a qualified generalist during his final year in medical school. He should be fairly convinced that first call for him is not a specialty, teaching or research. He should carefully select the community, or type of community, in which he desires to practice and he should allow himself at least two and probably three years of hospital training. If circumstances make it necessary to spend only a year in hospital training, he should be prepared, while practicing, to spend the first three to ten years in intensive postgraduate study.

For those who voluntarily enter the field of general medicine, who really like their fellow beings and wish to serve them and who are willing to make more sacrifices than most persons are called on to make, general medicine can, if properly conducted, be as rewarding as any special field.

MEDICAL PROGRESS

MYASTHENIA GRAVIS (Concluded)

Henry R. Viets, M.D.*

BOSTON

Treatment

Myasthenic Crises

Randt[50] summarizes the treatment of myasthenia gravis, particularly the handling of patients with myasthenic crises. This he describes as an inability to maintain pulmonary ventilation in spite of increasingly large doses of neostigmine, owing to weakness of the respiratory muscles, obstruction of the airway from weakness of the laryngeal or pharyngeal musculature or atelectasis and pneumonia from inability to expel secretions. States of this type may be precipitated or contributed to by overdosage with neostigmine, which is known to have a curarizing effect, with directly opposite results from those desired to maintain life. Randt believes that patients not responding to several doses of neostigmine methylsulfate, 2 mg. given deep subcutaneously, or those with signs of neostigmine intoxication and not responding to reduction in dosage, with inability to maintain proper pulmonary ventilation, may be precipitously withdrawn from neostigmine and placed in a respirator after an elective tracheotomy has been done. He treated 7 patients in myasthenic crises of this type, ranging in age from fourteen to seventy-five years, with duration of illness from four months to four years. Of the 7 patients 4 were able to carry on relatively normal activities in their homes after discharge, 1 died on the seventh day in the respirator, and 2

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others died after several months of intermittent respiratory care.

Crises of the type described by Randt are unusual. The method of treatment advised by him—namely, the withdrawal of neostigmine and the use of a respirator—appears to be justified in some cases although further experience is needed to be certain that this is always the best way to handle a desperate situation. The fact that 4 out of 7 patients survived the severe myasthenic crises is evidence that the procedure was a sound one.

Octamethyl Pyrophosphoramide

Gregory, Futch and Stone[51] found octamethyl pyrophosphoramide useful for oral administration because of its prolonged and uniform action, its chemical stability, absence of toxic effects and ease of determining maximum dosage. Fifteen out of 16 patients had less limitation of activity than after the use of any other drug. Dispensed as a 1 per cent solution in propylene glycol, the dosages were measured from 14 to 36 mg. a day (average of 24 mg.) in a dry tuberculin syringe. Before administration it was diluted in a few ounces of water or fruit juice.

Wilson, Williams and Miller[52] warned of overdosage, leading to "cholinergic crisis." The patient may die if not treated promptly with atropine, which may be given intravenously in an emergency in doses as high as 1.3 to 2 mg., as in "nerve-gas" casualties, which are in fact cholinergic crises.

Schulman, Rider and Richter[53] reported some advantages in the use of octamethyl pyrophosphoramide, such as the easy control by atropine of muscarine side effects. The disadvantage results from the difficulty in estimating an increase in weakness in terms of too much or too little of the drug. They found that the toxic weakness could appear suddenly and progress rapidly to fatal, generalized paralysis—the same hazard noted by Wilson and his associates.[52] The dose should not be over 30 mg. a day. Schulman et al.[53] could not endorse its general use without strict qualifications. Treatment should be restricted to patients with mild symptoms for whom neostigmine is not satisfactory.

These reports indicate that the drug can be used with caution. It has some advantages over other forms of medication. On the other hand its preparation is so hazardous that the makers have withdrawn it from the market. Some patients will miss it, but most clinicians will be relieved of the heavy burden entailed in the use of a potentially dangerous form of medication.

ACTH and Cortisone

Torda and Wolff[54] administered 500 mg. of ACTH to each of 15 patients and found that significant partial remission of long duration was established in 10. Only 4 cases were severe, 5 moderate, and 4 mild; 2 other patients were used as controls. During the administration of the drug most of the patients became weaker, and 1 died on the third day. Further treatment induced additional remissions. The effects could not be duplicated fully by the use of cortisone.

Merritt[55] reviewed the literature, including the study of Torda and Wolff, and found that in the majority of cases there was temporary exacerbation of the symptoms during the period of therapy, followed by a remission. The remissions were rarely complete and were temporary, lasting only a few weeks to several months.

Grob and Harvey[56] used both ACTH and cortisone. They reported exacerbation during administration, and in no patient was there any significant improvement in the myasthenia gravis either during or after the use of hormones. In 1 patient, moreover, who was taking cortisone for rheumatoid arthritis, myasthenia gravis developed during the seventh month of administration.

Pyridostigmin

A pyridine homologue of neostigmine has been given a therapeutic trial. Seibert[57] treated 23 patients. The drug was reported to be, in animals, five times less toxic than neostigmine, and the intestinal stimulation was only half that of the older drug. In patients the action was more prolonged than that of neostigmine, and the improvement in muscular strength was superior. Neck, trunk and muscles of the extremities showed more improvement than the muscles supplied by the cranial nerves. The dosage was three or four times that of neostigmine, 60 mg. being approximately equivalent to 15 mg. of the older drug. In general Seibert regarded pyridostigmin, given orally, as definitely superior to neostigmine in overcoming the symptoms of myasthenia gravis.

Sutter, Jorda and Lebascle[58] were somewhat less enthusiastic but found that pyridostigmin gave the best results when used clinically in combination with neostigmine. It appears that pyridostigmin, with its lesser effect on the intestinal tract, will have a definite place in the treatment of myasthenia gravis, not as a replacement for but as an adjunct to neostigmine.

Carotid-Sinus Denervation

The work on denervation originated by Thevenard in Paris in 1943 has been continued by him. Thevenard, Leger and Marques,[59] following 13 patients, reported that 1 was cured, 7 improved (3 considerably), and 5 not benefited. They believed that carotid-sinus denervation is never an emergency procedure and should not be attempted in all cases. It is indicated in patients who do not respond well to medical treatment and who have frequent relapses.

Stepien and Herman[60] operated on 10 patients. Two were considerably and 6 distinctly improved, and 2 received only slight benefit from the operation. The authors reported their best results in the more serious forms of the disease and concluded that every

case of myasthenia resistant to conservative treatment should be treated by this method. Thymectomy was rejected as too dangerous and uncertain an operation. A bilateral removal of the adventitia from the sinus was preferred.

The operation, not being on a sound physiologic basis, as pointed out by Bekaert,[61] has been little used outside France. Until more reports are at hand it cannot be recommended. The results are minimal and not definitely different from those seen in the normal course of the disease.

Other Forms of Treatment

Buscaino and Redi[62] reported that antireticular cytotoxic serum (Bogomolet's serum) overcame the ptosis and diplopia in a patient with myasthenia, but these observations have not been confirmed by others.

Granirer[63] used post-partum plasma, 200 cc. intravenously, repeated in a week, with improvement after the second treatment. He believed that the serum contains an enzyme capable of inactivating a "curare-like substance" in the myasthenic patient. This form of treatment, in the experimental stage, also requires a more extensive report before it can be accepted.

General Reviews

Turner[64] reviewed 100 cases seen at St. Bartholomew's Hospital in London. The series conformed to the standards of diagnosis and treatment now well recognized as the result of similar reports. Schlezinger[65] surveyed the various forms of therapy in 65 cases, Hoefer, Aranow and Rowland[66] in 156, and Grob and Harvey[67] in 220. These large groups, carefully analyzed, form a basic pattern with only slight variations. As Osler, quoted by Grob and Harvey,[67] stated in 1885: "It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusion the accumulated facts seem to point; and to ascertain in what direction we may look for fruitful investigations in the future." Each review helps to point up "fruitful investigations."

Myasthenia Gravis and Pregnancy

Fraser and Turner[68] studied the course of the disease during pregnancy in 14 women, who became pregnant after the disease was established. The course varied: 2 experienced no change; 1 was slightly improved in the last five months; the disease progressed in 4; remissions occurred in 2; 4 were symptomless; and 1 patient, who had had two pregnancies, had a complete remission after deep x-ray therapy at the third month of the first pregnancy and a relapse in the second month of the second pregnancy. Labor was relatively normal. Of 7 infants born in the hospital 1 gave evidence of myasthenia. The authors found no medical indication for termination of pregnancy. The greatest danger was a relapse in the post-partum period, especially during the first three weeks. Because of this, hospitalization was advised. Neonatal myasthenia in the infant subsided in three weeks.

This excellent paper conforms to currently accepted standards, although in the only other series reported (Viets et al., in 1942) more remissions were obtained during the second and third trimesters. This was also true in the case reported by Shade and Foley.[69] It appears that, although the course of the disease may be affected by pregnancy, the deviation is not always marked. Patients more seriously ill show greater tendencies to remissions during pregnancy. Four of the patients of Fraser and Turner[68] were symptomless at onset and remained so.

Hyperthyroidism and Myasthenia Gravis

Millikan and Haines[70] found both clinical and pharmacologic evidence that myasthenia gravis and hyperthyroidism are separate diseases. The administration of neostigmine did not change the weakness of hyperthyroidism. Patients with hyperthyroidism showed a normal response to injections of curare, whereas those with myasthenia gravis were highly sensitive to the drug. There was no consistent relation between the two diseases, an opinion now commonly accepted by most clinical investigators.

Levy, Meadows and Gunnar,[71] reporting 5 cases of both diseases, regarded the association as not very uncommon. The treatment of the thyrotoxicosis had no effect on the myasthenia gravis. Neostigmine, on the other hand, did not help the thyroid symptoms.

Althoff and Floer[72] found the two diseases in a five-year-old girl. Both conditions responded to appropriate treatment.

Hatch[73] showed that exophthalmos, frequently associated with hyperthyroidism, may also be part of the myasthenic syndrome and thus be relieved, like the other types of skeletal-muscle asthenia, by neostigmine. The mechanism of the exophthalmos in myasthenia is not known, but the response to neostigmine is clearly shown in the illustration accompanying the report of a single case by Hatch.

Zondek and Ticho[74] observed in a sixty-year-old man, who did not respond well to neostigmine, an increased basal metabolic rate (+ 20 to 28 per cent) not explained by hyperthyroidism. The response to propylthiouracil and to ACTH was not favorable, but irradiation of the pituitary gland, 3000 r in a period of five weeks, resulted in improvement, lasting until the patient was last seen five months later.

Miscellaneous Topics

Myasthenia Gravis and Anesthesia

The dangers of giving an anesthetic, such as Pentothal intravenously or inhalation ether, in an undiagnosed or subclinical case of myasthenia have frequently been emphasized. Nevertheless, Van Nouhuys[75] was able to add 3 cases from his own clinic to the 19 reported by Foregger[76] in 1950. He also

warns that myasthenia may be precipitated by a major operation, by the anesthetic or by both. In 1 of his cases prompt recognition of the disease was followed by neostigmine treatment. The anesthetist should be alert to the diagnosis, if the patient goes into deep anesthesia much more quickly than usual or with a smaller dose than average. In his patients only 0.4 gm. of Pentothal in 1 case and 0.5 gm. in another were needed to produce deep anesthesia; in other words the patient behaved as if he were curarized.

The fatal effects of muscle relaxants have also been referred to in many reports. In drugs of this class, curare (*d*-tubocurarine) is most frequently used but Flaxedil (gallamine) and decamethonium are also widely employed by anesthetists. As pointed out by Pelikan, Tether and Unna[77] patients with myasthenia gravis are five and a half times as sensitive to curare as nonmyasthenic persons. On the other hand the patient with myasthenia gravis is not more sensitive to decamethonium and appears to possess a tolerance to this drug[11] when the disease is localized. This tolerance is more difficult to demonstrate when the muscle weakness is widespread. Thus, even decamethonium must be used with caution, particularly if myasthenia is suspected from the history or the examination. An alert anesthetist should seek out any history of unexplained muscular weakness before using a muscle relaxant.

Bergh[78] carried out studies on 12 myasthenic patients and on 20 nonmyasthenic controls, using quinine, curare, Flaxedil, decamethonium and succinylcholine. As in other reports quinine, curare and Flaxedil were followed by marked aggravation of the symptoms in the myasthenic patients. With decamethonium the muscle weakness was aggravated in 2 patients; in 2 others the reaction was only fairly mild and transient. With small doses of succinylcholine the response in 5 patients did not differ with certainty from that in the controls. Bergh suggested that succinylcholine is the drug of choice in the management of patients with myasthenia gravis.

The maintenance of the patient on neostigmine during operation and in the postoperative period is one of great importance. Before good control was established, the operative mortality was greatly increased by respiratory paralysis due to ineffectual support by neostigmine. In Viets's clinic the control is obtained by the use of neostigmine given intravenously by the drip method.[80] Keynes and others employ the intramuscular route, as Dauri[79] does.

Anderson, Churchill-Davidson and Richardson[80] observed a patient with myasthenia gravis that was not recognized before operation for carcinoma of the bronchus. Under thiopentone sodium, 0.5 gm., and succinylcholine, 50 mg., the patient had a marked period of apnea. Recovery occurred after an hour, without the use of neostigmine. In spite of the fact that the clinical history was most suggestive of myasthenia gravis a diagnostic test was not done, although the classic symptom of muscle weakness with recovery on rest had been present in the legs, arms, neck and extraocular muscles, along with transient dysphagia.

Parathyroidectomy

In a case reported by Akao and Kawaishi,[81] Kawaishi, professor of surgery at Hiroshima Medical College, removed the parathyroid glands in a five-year-old girl with undoubted myasthenia. Before operation the neostigmine test was positive. The authors stated that the patient was much improved in three months. This appears to be the only report on parathyroidectomy in the literature.

Orthopedic Aspects of Myasthenia

Tether[82] calls attention to the possibility of myasthenia in patients with faulty posture and gait due to weakened muscles, and gives examples of 15 patients whose chief complaints were primarily orthopedic. He has seen a total of 170 patients with myasthenia gravis in his clinic in ten years. The mortality rate was only 3.5 per cent.

Complicating Diseases

Schantz[83] found myasthenia in a patient who also had diabetes mellitus, intraventricular block and pulmonary tuberculosis. There appeared to be no relation between myasthenia and the other conditions.

Williams and Silbermann[84] reported a case of myasthenia complicated by schizophrenia. Electric-shock therapy was given without difficulty, and the myasthenic symptoms were not affected by this treatment.

Histology of Muscle

Russell[85] described the histologic changes found in muscles obtained in 8 patients. Four of the patients had thymomas. Brief but adequate case histories accompanied the paper. The pathologic changes were of three different types; an acute change in which fibers underwent necrosis, with resulting inflammatory cellular reaction, and then disappeared; a progressive atrophy of the individual fibers associated in the later stages with the formation of lymphorrhages; and, finally, a simple type of atrophy of a different character from that seen in the second type affecting single fibers or groups of fibers.

Russell concluded that the changes, which were found in patients both with and without thymoma, were important in relation to the clinical evidence of muscular dysfunction. She believed, however, that the muscle atrophies were not peculiar to myasthenia gravis and not of diagnostic importance. Although most of the studies in recent years have concerned the nature of the chemical disturbances at the myoneural junctions, the substantial pathologic changes found by Russell in the striped muscles indicate that this aspect of the disease cannot be denied.

"Malignant" Thymoma

Katz[86] reported on a male patient with a malignant thymoma who died while under treatment in a respirator. At autopsy a huge tumor was found in the chest, the superior mediastinum being completely obliterated by the mass, which also extended down between the pericardium and the right lung. The tumor had infiltrated the right pleura and obliterated the pleural space. Although the great vessels, the trachea and bronchi were covered by the mass no compression or invasion was noted. On microscopical examination the tumor consisted of epithelial cells with scattered masses of lymphocytes throughout. Many mitotic figures were seen. There was evidence of radiating fibrosis of the pleura and pericardium, the patient having been given x-ray therapy. There was no evidence of distant metastasis, but there was some erosion of the chest wall by direct extension. The peritoneum was also invaded through the diaphragm. These findings, which are in accord with the experience of others, indicate that tumors of the thymus are not malignant in the sense that they produce distant metastases.

Large Doses of Neostigmine

Rider, Pickett and Harrison[87] gave an eighteen-year-old girl 84 tablets of neostigmine (1260 mg.) in twenty-four hours, without evidence of toxicity. During operation for the removal of a simple hyperplastic thymus neostigmine was given intramuscularly in doses of 1.5 mg. of the methyl sulfate every hour. In spite of this dosage myasthenic crisis developed after operation, and the medicine had to be increased to 3.5 mg. every fifteen minutes. With the aid of a respirator and an intratracheal tube, the patient improved on the second postoperative day. Recovery was slow, but she was discharged on 20 tablets a day. Other patients have taken even larger doses of neostigmine. The fatal dose is not known. Full maintenance in a very severe case may require 2000 mg. or more, given orally, in twenty-four hours. Large doses for parenteral administration are more conveniently given intravenously than intramuscularly.

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MEDICAL INTELLIGENCE

MEDICOLEGAL APPLICATIONS OF BLOOD GROUPING*

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ONE of the branches of medical science that has undergone rapid expansion in the last decade is that of immunohematology, or the study of the blood groups and blood-group antibodies. In this new specialty, the accumulation of detailed knowledge of genetic composition on the basis of the blood groups present in red cells has led to unusually practical clinical and medicolegal concepts.

Through the careful use of specific antiserums various blood groups and types are now susceptible of precise determination, and it has been well established that the ordinary laws of heredity operate in regulating the presence or absence of each of the blood-group factors in different persons. These blood groups never change during life; also, by the laws of genetics, it can be categorically stated that a person may never possess a blood-group factor lacking in both of his true parents.

With these two well proved rules as basic laws it can be seen that the blood-group systems can be used to provide evidence of identity or to resolve questions of disputed kinship.

The application of blood-grouping technics to medicolegal questions requires certain general and specific knowledge, and it is particularly timely to consider this at present.

The *General Laws* of the Commonwealth of Massachusetts, Chapter 273, now contain a provision,[1] effective June 23, 1954, that in cases of disputed paternity the court is required, on motion of the defendant, to "order the mother, her child, and the defendant to submit to . . . blood grouping tests. . . . " The results of such tests are admissible in evidence, but only when the blood tests show that the defendant is not the father. Refusal of the mother to submit to the tests is considered prejudicial to her case. Before the passage of this legislation, though the results of blood-grouping tests were accepted in the courts of Massachusetts, the tests could be done only if the mother agreed voluntarily to submit to them, and since she had very little chance of substantially strengthening her case by so doing, and could refuse without prejudice, she would ordinarily have been well advised to refuse. The new act is a real aid to justice, since in cases of men falsely accused, proof of nonpaternity, with the blood-grouping procedures presently possible, can be expected in about 53 per cent. It is believed that this percentage will be raised considerably in the foreseeable future, as explained below.

In addition to cases of disputed paternity there are two situations in which the performance of blood-grouping tests can be of medicolegal value. One of these is in alleged interchanges of infants such as might occur in a hospital nursery. In such a case the presumption of interchange would be demonstrated if either the father or the mother (or both) could be excluded as the parent of the infant in question. With serums presently available this is possible in about 80 per cent of cases. The third medicolegal application involves individual identity, for it is now possible in most cases (99 per cent) to distinguish between two persons by blood-grouping tests if all the available serums are used.

Another useful application of blood grouping applies to twins—if twins are not identical (monovular twins) a difference in one or more of the blood-group factors can usually be demonstrated (87 per cent). Since it is frequently important in medical research to prove as nearly as possible that apparently identical twins are in fact identical the evidence that blood typing provides is of great value.

Table 1 lists the important blood-typing antiserums that have been identified up to the present and indicates the blood-group "family" or "system" to which each belongs and the relative usefulness of each test or group of tests in the various problems that have been mentioned. The footnote to the table shows the effectiveness of large combinations of these reagents.

EXCLUSION OF PATERNITY

Testing for possible exclusion of paternity requires the highest degree of accuracy. In addition, for results of the tests to be acceptable in courts of law, the inheritance of the blood-group factors under investigation must be known absolutely and demonstrated by a large body of data on families. For these reasons, only anti-A, anti-B, anti-C, anti-D, anti-E, anti-c, anti-M and anti-N have been universally accepted in this country in exclusions of paternity. Tests with anti-A_1, anti-S, anti-C^w, anti-e, anti-f and anti-K, although they do not have the same background of medicolegal acceptance as the other tests, can provide valuable evidence. In time, most if not all of these

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will be generally acceptable. Anti-Fy[a] serum and most of the others following it in the list will eventually be available in sufficient quantities, and of sufficient potency and with a large enough accumulation of genetic data to be generally useful. It is almost certain, moreover, that new blood-group antibodies will be identified in the future, and each new discovery will make it more likely that a falsely accused man can be acquitted by the blood typings. If the tion of specimens may be important, but freezing must be avoided. It is best to have the bloods drawn in the laboratory where the blood-grouping tests are to be done. It will be essential for some years to come that blood-grouping tests for exclusion of paternity be done in the few laboratories where specially trained technicians, a considerable variety of serums and the knowledge of serology and genetics necessary for the interpretation of the results are available.

TABLE 1. *Important Blood-Typing Antiserums.*

Blood-Group "System"	Typing Reagents Used	Approximate Average Chance* of Exclusion of			
		Paternity, when man is falsely accused	Parentage, in cases of actual interchange of infants	Identity, in cases of non-identical twins	Identity, between two unrelated persons
		%	%	%	%
A-B-O	Anti-A,-B	14	25	33	60
A-B-O	Anti-A_1	3	6	5	15
M-N-S	Anti-M,-N,-S	23	36	52	80
Rh	Anti-C,-C^w,-c,-D,-E,-e,-f	35	50	52	80
Kell	Anti-K	4	8	9	18
Duffy	Anti-Fy^a	5	8	26	45
P	Anti-P	3	5	22	39
Lutheran	Anti-Lu^a	3	7	7	14
Kidd	Anti-Jk^a	3	4	21	35
Lewis	Anti-Le^a,-Le^b	5	5	25	35
M-N-S	Anti-s	11	15	8	18
Kell	Anti-k	<1	<1	<1	0
Duffy	Anti-Fy^b	14	21	19	30
Kidd	Anti-Jk^b	16	25	25	42
Combined, by tests presently practicable and reliable		53	79	87	99
Combined, all antiserums listed (many not available at present)		79	92	98	99.956

*Following are the page references in the book of Race and Sanger[2] for gene, genotype and phenotype frequencies used in above calculations: 19 (Dobson & Ikin—A,B,O), 19 (Ikin et al.—relative frequencies A_1 and A_2), 51 (M-N-S), 84 (Rh), 181 (Sanger et al.—K,k), 206 (Duffy), 66 (London, Sanger et al.—P), 175 (combined, Lutheran), 202 (Andresen-Lewis). Kidd frequencies from Race et al. (*Nature* 168:207, 1951).

ability to disprove paternity in the case of falsely accused men ever approaches 100 per cent, virtual proof of paternity in cases in which the man is actually the father will frequently be possible. At present it would be rare for the blood types to be such that the findings would be tantamount to proof of paternity. As Race and Sanger[2] have stated:

> On rare occasions paternity could be proved beyond all reasonable doubt. If, for example, an accused man and the child were both . . . [of certain very rare groups] . . . and the mother was of common groups, paternity would be proved, provided that the brothers of the accused had alibis. Outside the family of the accused there would not be another such man in ten million.

In the handling of blood samples utmost care must be used to assure the identity of each specimen (as well as the identity of the person from whom it is drawn) and its prompt delivery into the hands of the person who is to do the tests. Precautions must be taken to assure that no one tampers with the specimens. Dry, sterile equipment is necessary. Refrigera-

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FATAL HEPATITIS AFTER PHENURONE THERAPY FOR EPILEPSY*

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IN 1948 Phenurone (phenylacetylurea) was introduced for the treatment of psychomotor epilepsy. Early reports[1-5] of its use were favorable, but reports

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of toxic side effects began to appear and several deaths from liver failure[4,6,7] were attributed to it. Because there has been no recent report on the toxicity of this drug, the following case of fatal hepatitis after treatment with Phenurone is presented.

Case Report

Mrs. L. S. (M.G.H. 805317), a 39-year-old housewife, was admitted to the Massachusetts General Hospital from an out-of-state hospital on March 18, 1953.

In September, 1949, she began having attacks during which she stopped whatever she was doing, stared into space and mumbled confusedly for several minutes. In the summer of 1951 her friends noted slight changes in her personality. At that time a neurologic examination was negative, though an electroencephalogram revealed spikes and slow waves in the left anterior temporal region. A diagnosis of psychomotor epilepsy was made, and she was treated with Dilantin in gradually increasing amounts, up to 0.4 gm. a day. Because this drug was ineffective Phenurone therapy was begun in August, 1952. The initial daily dose of 0.25 gm. was gradually increased to 4.25 gm. One month later this dosage was reduced because of itching and drowsiness. She continued with the treatment, though she was not seen by her family physician until 4 months later, when she was confused and had obvious personality changes. Although she was not jaundiced toxicity was suspected. The urinary urobilinogen was "moderately positive," and the dosage was reduced to 3 gm. daily. One week later the urine showed a faint trace of urobilinogen, but because she was still mentally confused, the dosage was further reduced to 1 gm. daily. On this reduced dosage she felt much improved, and in January, 1953, the urine was negative for urobilinogen. In the following month she doubled the dose to 2 gm. a day, but 2 days later she reduced it to 0.5 gm. because she noted poor muscle co-ordination. Two weeks later the urine was again positive for urobilinogen. Soon afterward weakness, nausea, vomiting, anorexia, constipation and a gross tremor of the hands developed. In March, 1953, she became confused and jaundiced and was admitted to a hospital, where the Phenurone was discontinued.

On admission she was weeping and depressed and talked of irrelevant things. There was obvious jaundice. The liver edge was palpable at the right costal margin but was not tender. Urinalysis was negative for sugar and albumin, though rare hyaline casts and occasional white cells were noted in the sediment. Examination of the blood revealed a red-cell count of 4,140,000, with a hemoglobin of 11.7 gm. per 100 cc., and a white-cell count of 10,800, with a normal differential. The icteric index, which was 45 units on admission, rose to 141 units in 4 days. The alkaline phosphatase was 13.1 Bodansky units. The prothrombin time was 31 per cent of normal. The total cholesterol was 108 mg. per 100 cc. A stool gave a ++++ guaiac reaction. A Graham–Cole cholecystogram showed nonfilling of the gall bladder. No radiopaque calculi were demonstrated. On the 12th hospital day the patient was transferred to the Massachusetts General Hospital.

Physical examination disclosed a deeply jaundiced, drowsy and only slightly responsive woman. There were no spider angiomas or palmar erythema. The lungs were clear to percussion and auscultation. Although the heart was of normal size, there was a Grade 2, blowing systolic murmur, heard best at the base. The abdomen was distended. The upper border of liver dullness was at the 4th intercostal space, and the lower edge was palpable 1 cm. below the right costal margin and was nontender. The spleen was not felt. Neurologic examination was negative except for an inconstant tremor of the left hand. The temperature was normal.

The urine gave a strongly positive bile test, but was otherwise normal. The hemoglobin was 15 gm. per 100 cc., and the white-cell count was 9400, with a normal differential. The serum van den Bergh was 16.4 mg. per 100 cc. direct and 23 mg. total. The cephalin flocculation was ++++ in 48 hours. The alkaline phosphatase was 10.2 Bodansky units per 100 cc. The total protein was 5.5 gm. per 100 cc., with 3.1 gm. of albumin; nonprotein nitrogen was 18 mg. per 100 cc.

The patient was given a 3000-calorie diet by stomach tube and dextrose intravenously. She showed some slight improvement initially, but on the 3d hospital day the temperature rose to 101°F., and she lapsed into deep coma. The temperature remained elevated in spite of intravenous administration of chlortetracycline, and the coma persisted. There were no localizing neurologic signs. On the 6th hospital day she died, approximately 7 months after the initiation of Phenurone therapy.

At autopsy the body was intensely icteric. The liver, which weighed 1260 gm., displayed 2 striking gross features. The diaphragmatic portion of the right lobe was dull-brown red and extremely soft. The remainder of the liver was yellow tan and, though slightly firmer than the right lobe, was softer than normal. Occasional firm, tan-yellow nodules, measuring 3 or 4 mm., were apparent on the external and cut surfaces. There was no ascites. The spleen weighed 260 gm. and was of soft, pulpy consistence. The small intestine was collapsed and empty. The colon was filled with clay-colored fecal matter. The remainder of the gross autopsy findings were not unusual.

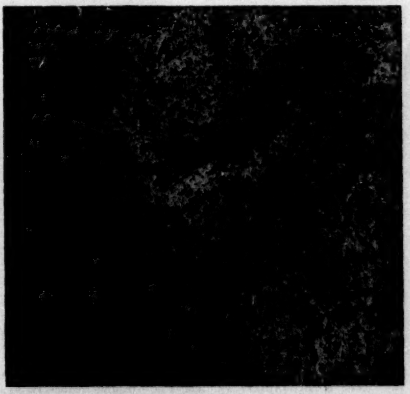

Figure 1. *Section from an Area of Softening, Showing Massive Destruction of the Liver Parenchyma. The only viable tissue is the collection of liver-cell cords.*

Microscopical examination of the liver showed diffuse involvement of all portions. Very little intact liver parenchyma was noted, and no normal lobules were identified. Sections from the diaphragmatic portion of the right lobe demonstrated massive devastation of all lobules in their entirety (Fig. 1). Other areas contained focal necrosis of liver cells, with a pattern suggesting a zonal localization of necrosis, beginning around the centrolobular vein and spreading peripherally toward the portal tract. The collapsed reticulum stromal framework in the completely devastated lobules created a picture that suggested an increase in portal-tract fibrous tissue. However, this was more apparent than real, for specific stains showed no increase of connective tissue. Occasional spheroid collections of regenerating liver cells were noted; these corresponded to the small tan-yellow nodules noted on gross inspection. The bile ducts gave evidence of regeneration, though this was not a prominent feature. Some bile ducts and bile capillaries were plugged with bile thrombi. There was both lymphocytic and neutrophilic infiltration into the portal tracts and lobules. Fat stains revealed a minimal amount of fat scattered throughout. Microscopical examination of other organs, including the kidneys, disclosed no unusual features.

Discussion

Although the possibility of viral hepatitis cannot be excluded the relation of the Phenurone treatment and the hepatitis is regarded as more than coincidental. Complicating hepatitis has previously been noted.[1-12] The interval between the initiation of treatment and death in this case was seven months—longer than that of previously reported fatal cases (seven weeks,[6] eleven weeks,[4] two months[7] and three months[6]). Definite untoward reactions from the drug, apart from the fatal hepatitis, included personality changes, muscular inco-ordination and gastrointestinal symptoms. During the therapy the urinary urobilinogen was elevated, a finding that is believed to indicate a hepatotoxic effect of Phenurone. Dilantin, which was the only other medicament given, probably had no connection with the liver failure.

It is suggested that all patients receiving Phenurone be carefully followed with tests of urinary urobilinogen and that the drug be stopped at the first sign of liver damage.

Summary

A fatal case of acute hepatitis, presumably due to Phenurone toxicity, is presented. A suggestion for avoidance of similar cases in the future is made.

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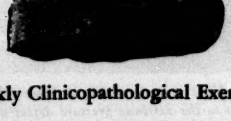
CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40291

Presentation of Case

First admission. A fifty-eight-year-old hospital attendant was admitted to the hospital because of epigastric pain.

About two months previously, when he came to the medical clinic, he said that three weeks earlier, several days after lifting a heavy object, he noted the onset of a vague, poorly localized epigastric pain, which seemed to originate subcostally and to radiate to the midepigastrium. The pain occurred mostly in the late evening and occasionally was sufficiently distressing to keep him awake during the night. Occasionally, the pain radiated to the back and left upper quadrant. It had no relation to position or food intake. An ulcer regimen was started, and he reported some improvement at first. Four weeks before admission the pain became increasingly severe and was not ameliorated by a bland diet, sedation, antacids and rest. For the week preceding admission the pain became so severe and constant that he was forced to stop work. There was no nausea, vomiting, hematemesis or melena. He had lost about 12 pounds in weight.

Twenty-three years previously the patient had had an episode of midepigastric pain, with vomiting after a meal. After x-ray studies he was told that he had ulcers and was placed on an ulcer regimen. Each year since then he had had one or two episodes of epigastric pain, which had always responded well to antacids and a bland diet. Although for the first ten days of the present illness the pain was similar to the old pain, it had changed in character and was now definitely different by virtue of its radiation. Eleven years previously he had been treated for three weeks for pneumonia. He had had no previous hospital admissions.

Physical examination revealed a thin, hyperactive man in no acute distress. The heart and lungs were normal. The liver edge was felt 2 fingerbreadths below the right costal arch, and the dome of the right lobe of the liver was percussed in the seventh intercostal space. There was minimal epigastric tenderness. No masses were felt.

The temperature, respirations and pulse were normal. The blood pressure was 124 systolic, 84 diastolic.

Urinalysis was negative. Examination of the blood

revealed a hemoglobin of 15 gm. per 100 cc. and a white-cell count of 8000, with 65 per cent neutrophils, 25 per cent lymphocytes, 4 per cent monocytes and 6 per cent eosinophils. The nonprotein nitrogen was 29 mg., the serum amylase 20 units, the total bilirubin 0.4 mg., the blood sugar 107 mg., and the alkaline phosphatase 3.8 units per 100 cc. The serum lipase was 0.5 cc. A bromsulfalein test showed 6 per cent retention of the dye after one hour. A blood Hinton test was negative. Stool specimens were repeatedly guaiac negative. An electrocardiogram showed a normal tracing. A roentgenogram of the chest disclosed a few calcific densities in the right apex, and to a lesser extent in the left. The heart was of normal size and shape. Mild arthritic lippings were noted in the mid-dorsal and cervical spine. A barium-swallow examination demonstrated a normal esophagus and large gastric rugae in the midportion of the greater curvature, whose pattern was bizarre. No antral spasm was noted. The duodenal bulb was scarred, but no ulcers were noted. Several areas suggested superficial erosions within the bulb. The duodenal loop appeared normal. A second barium-swallow examination one week later showed the same changes. In a Graham–Cole test there was excellent concentration of the dye, and no stones were seen. An intravenous pyelogram was normal, as was the bladder contour. Gastric aspiration revealed a 37-cc. fasting sample, with 3.5 units of free acid (10 units per 100 cc.) and 17.2 units of combined acid (46.4 units per 100 cc.). A cytologic examination of gastric lavage was negative for tumor cells. Gastroscopic examination disclosed hyperactive peristalsis but no other abnormalities; a biopsy of the anterior wall of the stomach was negative.

The patient was treated with an extremely rigid ulcer regimen, but except for rare interludes lasting several hours he had continuous, burning epigastric pain that radiated laterally beneath the ribs. The pain was most intense in the early morning hours, awakened him from sleep and was relieved only by codeine. A psychiatrist evaluated the patient as tense and hypochondriac, with an immature and dependent personality; the behavior was consistent with a chronic, severe, mixed neurosis that tended to exaggerate symptoms that could have been organic. He was discharged on the twenty-fifth hospital day at his own request almost completely free of pain. He was given sedatives, a bland diet and antacids. He had remained afebrile during the hospitalization.

Second admission (one month later). After discharge from the hospital the pain had persisted unabated. It was worse at night and was little affected by medication. The pain had shifted to slightly below the umbilicus. The patient stated that the pain had made him very nervous, that his "nerves were all shot" and that he "had to get a hold on himself." He had lost his appetite. There had been an additional 3-pound weight loss in the week before admission.

Physical examination was unchanged except for mild guarding of the upper abdomen. The urine was normal. The blood hemoglobin was 12.5 gm. per 100 cc., and the white-cell count 7000. The serum amylase was 39 units per 100 cc. A stool specimen was guaiac negative. A barium-swallow examination showed thickened folds of the body of the stomach and a deformed duodenal cap (Fig. 1). No ulceration was demonstrated. A barium-enema examination was negative.

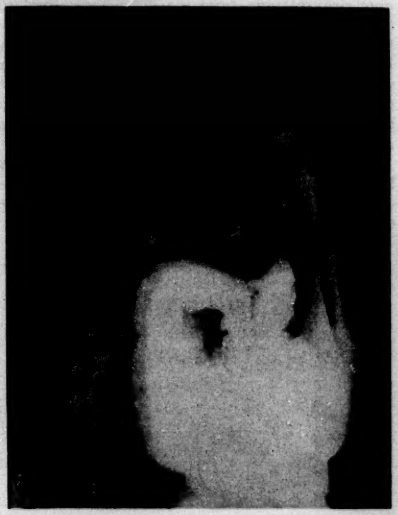


FIGURE 1. *Right Anterior Oblique View of the Stomach. Arrows point to the extrinsic pressure defect on the posterosuperior aspect of the stomach wall.*

On the second hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. F. DENNETTE ADAMS*: Dr. Morgan, I have a few questions. Was the rectal examination negative?

DR. WINFIELD S. MORGAN: The prostate was reported as being twice the normal size.

DR. ADAMS: Since weight loss may be an important clue to the diagnosis I am anxious to learn if the patient gained weight during his hospital stay. Or was there continued loss?

DR. MORGAN: There was progressive loss of weight while he was in the hospital.

DR. ADAMS: There are two contradictory statements in the protocol: he is said to have been "almost completely free of pain" at the time of discharge,

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and yet, three sentences later, we are told that after discharge, the pain "persisted unabated." Which is correct?

DR. MORGAN: I have the impression that he was almost completely relieved of pain at the time of discharge but that the pain soon recurred.

DR. ADAMS: He could not have been "almost free of pain" for any appreciable period. He was discharged at his own request. One cannot but wonder if the pain in his pocketbook was not greater than that in his abdomen. He was on an ulcer regimen in the hospital for almost four weeks. Could it be that he thought he could do equally well at home at much less expense and thus, for a while, minimized his pain in order to be discharged? Since this is a teaching exercise I pose this question primarily for the younger members of the audience — those who have not yet had the experience of private practice. Those who later go into this field must always be alert to the problem of staggering hospital bills superimposed on loss of income incident to absence from work. So it may be that this man, in spite of his alleged hypochondriasis, stretched the truth in reporting that his pain was better. With these facts in mind, especially the statement that the pain continued unabated, I am going to proceed on the premise that it was virtually persistent — that he had intractable pain in the upper abdomen for a period of four months. We all agree, I am sure, that surgical exploration was indicated. It is my assignment to try to determine what the surgeon found. There appears to me to be only one likely diagnosis, which I shall eventually make without reservation, but with full realization that it is a hazardous venture in an exercise of this kind. What are regarded as other but more remote possibilities will be discussed for the record.

The physical examination, laboratory and x-ray studies are helpful in a negative sense. They give us no positive clues but are of assistance in excluding certain possibilities. One cannot account for the 6 per cent eosinophil count, which was observed only once. The statement that the right lobe of the liver was percussed in the seventh space is worth a word of comment. This is unusual in the absence of emphysema or a large pneumothorax on the right, even in a patient who is thin and has lost considerable weight. I believe that x-ray films will show emphysema and a low diaphragm, but no liver enlargement. Dr. Hanelin, can we now check up on the lungs and liver as a matter of interest and then have your comments on the other studies?

DR. JOSEPH HANELIN: The lungs are clear and somewhat emphysematous. There are a few calcified scars at the bases, particularly on the right side. Four gastrointestinal examinations extending over about a three-month period were done; all were reported as showing no intrinsic disease except for a deformity of the duodenal bulb. At no time were any of the examiners convinced of the presence of an active ulcer, nor do I see any evidence of an active crater in these films. The deformity of the duodenum, however, is characteristic of scarring from an old ulcer.

DR. ADAMS: No spasm was observed at fluoroscopy.

DR. HANELIN: I suspect gastric emptying was fairly rapid. One thing I might call attention to on these films is a suggestion of slight extrinsic pressure on the body of the stomach along the posterior aspect of the lesser curvature, just below the level of the fundus (Fig. 1).

DR. ADAMS: That last observation is not in the protocol; it tends to lend me both support and courage. The plain films show no enlargement of the spleen or liver?

DR. HANELIN: The spleen is normal in size; the liver may be slightly enlarged from these films. The pyelogram appears quite normal. There is a normal cholecystogram, with well concentrated dye in the gall bladder, and a perfectly negative appearing barium-enema examination.

DR. ADAMS: Since, as indicated earlier, only negative help is obtainable from other studies, we are forced to rely on history and history alone. I am fortunate that the symptoms are well recorded. This part of a case analysis is most often the least well explored; more diagnoses are missed because of failure to take or to evaluate a history with care than for any other reason.

In essence this was intractable and virtually persistent pain in the upper abdomen, with little else to go with it. The statement that it occurred four or five days after lifting can be disregarded. If it had started immediately after such a strain, one would be forced to consider some mechanical factor — perhaps a tear, or the breaking-loose of protective adhesions around an ulcer. Here the interval of time excludes this necessity.

Furthermore, at the risk of being regarded as not aware of the importance of the psychogenic origin of pain or other symptoms, I must also discount the erudite psychiatric survey of this case. This man may have had an immature personality; he may have been dependent on others. But his performance history is not bad. One notes that he had had symptoms that were presumably due to ulcer once or twice annually for twenty-three years but only one previous hospitalization, and that for pneumonia. That is not the story of hypochondriasis as it appears in my office many times a week. If he had received some acute emotional insult immediately before the onset of pain, one would be forced to give greater consideration to psychogenic factors. Furthermore, there were no other symptoms such as one would expect with hypochondriasis, and the pain kept him awake at night. Often, when related to an emotional disturbance, symptoms stop work with onset of sleep. The story of improvement can also be minimized for the reasons stated earlier. On three and a half weeks of a carefully regulated ulcer regimen, under what we can assume

were ideal medical conditions, the symptoms did not improve appreciably, and, of greater importance, he continued to lose weight progressively.

Intractable pain in the upper abdomen requires consideration of a number of disturbances; most of them can be promptly eliminated. Lymphoma must always be on the list — pain due to diseased intra-abdominal lymph nodes. There is absolutely nothing to go with them — no anemia, fever, enlarged lymph nodes elsewhere, abdominal mass or enlargement of liver or spleen. Lymphomatous nodes can appear alone in the abdomen and cause pain, but this is not too common.

What about some biliary-tract disturbance? Again, there is no evidence.

Next on the list is the stomach. The possibilities are cancer, ulcer and gastritis. Cancer seems out of the picture. If this had been an ulcerative or hyperplastic growth either the radiologist or the gastroscopist, or both, should have seen it. The only type of cancer that could be so thoroughly overlooked by both procedures is a scirrhous carcinoma, which does not cause such profound pain. Loss of appetite, indigestion and vague symptoms—nausea or revulsion against certain foods previously enjoyed — are the rule. One watches a patient with a scirrhous carcinoma, obtains few specific leads and wonders whether or not exploration is indicated. Eventually, the roentgenologist may detect rigidity, or perhaps the gastroscopist will see something awry. But even then pain is not prominent.

Gastric ulcer seems well excluded by x-ray and gastroscopic examinations. If ulcer was present, it would most probably have been a penetrating posterior-wall duodenal lesion, which, I think Dr. Hanelin will agree, can at times be overlooked by the roentgenologist.

DR. HANELIN: I think at times any lesion may be overlooked. Generally, we are able to see a penetrating ulcer or should see it.

DR. ADAMS: The boring pain that radiated to the back definitely introduces the possibility of posterior-wall ulcer, but even one that is penetrating gets somewhat better under treatment. The good treatment that this man presumably had should have reduced his pain appreciably. Discomfort, or what one might call awareness, could have continued, but severe pain should have been alleviated by the measures taken.

What was said about cancer can also be applied to gastritis. With this disease he would have had more indigestion, not the pain described. And the roentgenologist or gastroscopist would have seen changes.

We now come to the pancreas. There are only two possibilities: chronic pancreatitis and cancer. Chronic pancreatitis is an intermittent disease until it gets to the stage of fibrosis. At first, there are recurrent attacks of acute or subacute trouble, with severe bouts of epigastric pain, nausea and vomiting. Between times freedom from symptoms is the rule. Later, low-grade chronic pain may be present, but loss of appetite, indigestion, malnutrition, steatorrhea and other changes in the stool predominate. Calcium deposits may be detected on x-ray examination.

So, partly by the process of exclusion but more so from the description and progress of this man's illness, I come to a definite diagnosis of carcinoma of the pancreas. Having said that I shall go farther and say that the tumor was east of the head of the pancreas. Why? The intractable pain, which first simulated that of ulcer, started in the epigastrium, then reached the back, eventually spread to become periumbilical and defied treatment, is typical of carcinoma of the body or tail of the pancreas. Persistent loss of weight throughout the period of four months is also of great significance. Barring severe diabetes, starvation and a few other obvious causes, I know of nothing more certain than cancer of the pancreas to create progressive, relatively rapid weight loss. Furthermore, the patient with this disease often has "hypochrondriac" symptoms, and hence is thought to be psychoneurotic or at least to be exaggerating his pain. This circumstance may be related to the fact that, with negative x-ray and other studies, the physician cannot find its source. The long duration without any improvement that often marks a case of this kind may well lead to loss of pain tolerance and suspected "exaggeration" of symptoms. The lack of specific help from other sources—laboratory and x-ray studies—also tends to support the diagnosis of pancreatic tumor; so does the slight evidence of external pressure on the stomach that Dr. Hanelin has described.

To make a decision in retrospect is always easier than to make one at the moment. So, with some hesitancy and absolutely no intent to criticize those who handled this case, I must state my opinion that exploration might well have been undertaken sooner. I am here to think out loud as I should have thought about this man if he had been a patient of mine. It is my belief that, with his history, with all studies negative and with little relief from treatment, I should have suspected cancer after his first three weeks in the hospital and proceeded accordingly.

There seems to me to be no diagnosis to make except cancer of the body or perhaps the tail of the pancreas.

DR. MORGAN: Dr. Bauer, what do you think this man had?

DR. WALTER BAUER: I think I should go along with Dr. Adams's diagnosis.

DR. GORDON A. DONALDSON: Is it not true that with cancer of the pancreas the pain is usually in the back?

DR. BENJAMIN CASTLEMAN: Certainly the first symptom in a high percentage of patients with cancer of the pancreas is pain in the back.

DR. ADAMS: In this protocol the pain is described as radiating to the back; I assumed that it went through to the back, and spread laterally. With cancer of the pancreas, pain often extends downward, even-

tually to involve the umbilical region; it goes lower than the actual site of the pancreas. That is due to the pressure on, or invasion of, the celiac plexus.

DR. STUART RAGLAND: Dr. Adams has covered the ground a great deal more rapidly and efficiently than many of the persons who saw this patient. I was the one who admitted him to the hospital on both occasions. In the beginning of his illness it was taken more or less for granted that this patient had an ulcer, but after the first admission when he had no relief from the vigorous therapy, which included Sippy powders on the hour around the clock, that diagnosis came into doubt. He was readmitted—I might say, not as soon as some of us would have liked—to the hospital and explored with the diagnosis that Dr. Adams has made. The blood pepsin was very high—in the range of duodenal ulcer.

CLINICAL DIAGNOSIS

Carcinoma of pancreas.

DR. F. DENNETTE ADAMS'S DIAGNOSIS

Carcinoma of body of pancreas.

ANATOMICAL DIAGNOSIS

Adenocarcinoma of body and tail of pancreas.

PATHOLOGICAL DISCUSSION

DR. MORGAN: Dr. Ferguson, will you describe the operative findings?

DR. IRA A. FERGUSON: After the induction of the anesthesia a lemon-sized mass could be felt high in the epigastrium. On opening the abdomen we exposed a stony-hard mass in the body of the pancreas that had involved the celiac axis and was wrapped around the superior mesenteric artery. It was thought that we could get the whole mass out until it was found that it was around the mesenteric artery. The tail of the pancreas, the spleen and about half the tumor were removed; the other half had to be left, because of its blood-vessel invasion.

DR. MORGAN: Although microscopical examination proved the tumor to be a fairly well differentiated adenocarcinoma, it had replaced much of the pancreas and had invaded nerves widely. This last finding undoubtedly explains the dominant nature of the pain in the clinical picture.

Regarding the pain, Duff* found that in 14 of 16 cases of carcinoma of the body and tail of the pancreas abdominal pain was the initial symptom. In contrast, in a similar group of 16 cases of carcinoma of the head of the pancreas, jaundice was one of the initial complaints in 13 and abdominal pain only in 5, and in these 5 pain had not begun more than a week before the appearance of jaundice.

*Duff, G. L. Clinical and pathological features of carcinoma of body and tail of pancreas. *Bull. Johns Hopkins Hosp.* 65:69-99, 1939.

CASE 40292

PRESENTATION OF CASE

A thirty-three-year-old woman was admitted to the hospital because of abdominal pain, nausea and vomiting.

Fifteen years previously the patient first began to have nonradiating epigastric pain occurring a few hours after meals that was relieved by milk and soda. The attacks of pain were episodic, with six or seven symptom-free months between episodes, and often followed an emotional upset. When the pain recurred she went on a bland diet, with frequent feedings, milk and Amphojel. Gastrointestinal series ten and three years before entry were said to have shown a duodenal ulcer. Four months before admission she had a severe attack lasting a week, after which she was symptom free until two and a half weeks before admission, when she was awakened from sleep by severe epigastric pain accompanied by nausea, which was relieved by Amphojel and milk. The next morning pain recurred, and she became nauseated and vomited copious amounts of fluid, which at first contained particles of food but later was clear. She continued to vomit for the next four days, when she suddenly became short of breath, noted numbness of the hands and fainted. She was admitted to another hospital and treated with intravenous therapy, blood transfusions and a soft diet. She remained in the hospital for ten days. After a few days the pain disappeared, and the nausea and vomiting stopped; she was symptom free on admission. At no time had she noted melena or hematemesis. She had lost 10 pounds in weight in the two and a half weeks before admission.

She had had severe backaches, associated with some nausea, intermittently for fifteen years. Fifteen years before entry a urinalysis revealed a ++ test for albumin and 10 red cells per high-power field in the sediment; intravenous and retrograde pyelograms were normal. Four years later a renal stone was removed from the left kidney after an attack of left-flank pain. One year before admission she had another attack of flank pain, which lasted all day and was followed by the passage of several clear stones in the urine.

Physical examination showed a thin woman; there were no abnormal findings.

The temperature was 98°F., the pulse 68, and the respirations 15. The blood pressure was 100 systolic, 64 diastolic.

The urine had a specific gravity of 1.011; the sediment contained 5 red cells per high-power field; a urine culture demonstrated no growth. Examination of the blood revealed a hemoglobin of 12.6 gm. per 100 cc. and a white-cell count of 6900, with 58 per cent neutrophils. The nonprotein nitrogen was 24 mg., the total protein 5.5 gm., the calcium 11.1 mg., the phosphorus 2.0 mg., and the alkaline phosphatase 14 units per 100 cc.; the serum chloride was 99 milli-

equiv., and the carbon dioxide 27.2 milliequiv. per liter. A twenty-four-hour urine specimen with a volume of 2590 cc. contained 410 gm. of calcium. A phenosulfonepthalein test showed 20 per cent excretion in five minutes, 60 per cent in fifteen minutes and 70 per cent in two hours. Gastric aspiration yielded 550 cc. of pale-yellow, curdy material. A stool gave a negative guaiac reaction. A gastrointestinal series disclosed a normal esophagus, a large, atonic stomach with a large amount of secretion in it and inability to pass any barium through the pylorus dur-

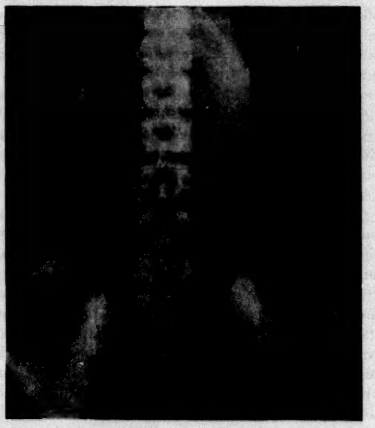

FIGURE 1. *Plain Film of the Abdomen, Showing Bilateral Nephrolithiasis, with the Most Conspicuous Calcifications within the Right Kidney.*

ing the period of examination, as well as retention of some barium in the stomach for twenty-four hours. An intravenous pyelogram demonstrated kidneys that were normal in size, position and contour. Numerous small renal calcifications were noted bilaterally; these appeared to be for the most part deposited in the renal parenchyma, but many appeared to be also in the minor calyxes (Fig. 1). There was slight diminution in renal function bilaterally, although at the end of ten minutes both pelves were well visualized. There was no evidence of hydronephrosis or hydroureter.

The patient was treated with frequent feedings of milk, custards and jello, atropine sulfate, Amphojel, daily gastric aspiration and supplementary intravenous therapy. After a week of treatment there was little improvement, and a gastric aspiration late in the evening still yielded 350 cc. On the tenth day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. STUART RAGLAND, JR.*: This patient had diseases involving two organ systems. Perhaps it will be best to discuss each separately and then to relate them to each other. In the first place there is a straightforward story of peptic ulcer starting at about the age of eighteen. The course of this disease was characteristically episodic, and it was not until two and a half weeks before admission that pyloric obstruction developed and required admission to the hospital. It is interesting in the light of what follows that after four days of vomiting enough hypochloremia and alkalosis apparently developed to result in tetany, which I imagine explains the episode of faintness and numbness of the hands. After this admission the patient became symptom free; however, it is interesting that although she was symptom free at the time of admission to this hospital there was x-ray evidence of continued pyloric obstruction. This suggests so-called gastric decompensation, with a large atonic stomach, and an absence of the characteristic ulcer symptoms. It would be interesting to know more precisely how much alkali and milk she was in the habit of taking in the fifteen years before admission, for this might have an important bearing on the second portion of the history, which deals with renal stones. Also, there is no information about which symptoms she had first — those of peptic ulcer or those of renal lithiasis.

I am given the interesting story of fifteen years or more of chronic renal disease characterized by albuminuria, microscopical hematuria, renal colic and recurrent renal lithiasis. At the age of twenty-two a nephrolithotomy on the left was performed. This was four years after the onset of the ulcer symptoms. At this point one must wonder if this was a case of primary renal disease made worse by the alkalinization acquired by coincident peptic ulcer, tubular acidosis with secondary hyperparathyroidism and duodenal ulcer, the Burnett syndrome[1] or a parathyroid adenoma with primary hyperparathyroidism and duodenal ulcer. The relation of duodenal ulcer to parathyroid overactivity is puzzling and interesting especially in view of the use of parathyroid extract in the treatment of ulcer by Levy and Levy.[2] At any rate I shall try to tie together the peptic ulcer and the renal stones.

On arrival at the hospital the vital signs and physical examination were apparently unremarkable; therefore, I shall assume that the patient was reasonably well hydrated and had no band keratopathy of the eyes and no palpable masses in the neck. Perhaps it would be well to look at the x-ray films now to see if there is any deviation of the cervical esophagus, any loss of lamina dura or general demineralization to go with the nephrocalcinosis.

DR. JOSEPH HANELIN: Some of the films have been lost and are not available for review. The abdominal film shows the stippled calcium deposits in the kidneys, greater in number and size on the right (Fig. 1), that for the most part appear to be in the renal parenchyma and outside the calyxes and renal pelves. Both kidneys excrete contrast medium in good concentra-

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tion, and normal, nondilated passages are demonstrated. The bones of the lumbar spine and pelvis have a somewhat coarser trabecular pattern than normal, suggesting decalcification. A single lateral view of the skull shows a mottled density of the vault that may be due to either Paget's disease or hyperparathyroidism, although more probably the latter. A full set of intraoral dental films demonstrate loss of the lamina dura about many of the teeth although it is preserved about some of them. There is a fair amount of alveolar absorption and thickening of the peridontal membrane; the loss of the lamina dura in this case was probably due to gingival and dental abnormality rather than to decalcification.

DR. RAGLAND: Unfortunately we do not have all the x-ray films; however, I assume from the description given in the protocol that the great size of the stomach and the atony are consistent with the diagnosis of pyloric obstruction secondary to duodenal ulcer, and I believe that with the history this description is against organic obstruction secondary to tumor. Spasm and edema are more probable causes of this obstruction than scarring. The films of the skeleton, although not conclusive, are consistent with demineralization. Despite the nephrocalcinosis demonstrated renal function appears to be good as judged by the intravenous pyelogram.

The other laboratory evidence should be considered. The hemoglobin of 12.6 gm. per 100 cc. is of little help. The patient had received an unknown number of transfusions in the fortnight before admission. A mild anemia may have been present, consistent with chronic renal disease or hyperparathyroidism, or she may have bled in the past although I do not think so. The blood chemical levels are more to the point. She had a moderate hypercalcemia associated with a normal total protein, a definite hypophosphatemia, an elevated alkaline phosphatase, a definitely high urinary calcium and a normal nonprotein nitrogen. The specific gravity of the urine was low; the serum chloride and serum carbon dioxide content were normal, and the phenolsulfonephthalein test showed a mild depression. The urine ammonia and pH figures and the serum sodium, potassium and pH were not mentioned.

In the absence of an elevated nonprotein nitrogen or other evidence of severe renal insufficiency and because of the hypercalcuria, hypophosphatemia and elevated alkaline phosphatase I can rule out the Burnett syndrome.[1] There was no evidence of tubular acidosis with secondary hyperparathyroidism except the presence of nephrocalcinosis, which may also occur in primary hyperparathyroidism and in some cases of pyelonephritis.[2] Since there was no mention of a urinary excretion of ammonia or of organic acids or of urinary pH I assume that the patient did not have this disease or that it was not considered on the service. I suppose that she may have had tubular acidosis with hypocalcemia to explain the symptoms two weeks before admission and that under vigorous treatment with alkali, the chemical values returned to normal, but this seems farfetched indeed. The findings of hypercalcemia, hypophosphatemia, high alkaline phosphatase, hypercalcuria, low specific gravity of the urine, nephrocalcinosis and nephrolithiasis make a diagnosis of primary hyperparathyroidism almost certain.

What operation was performed on the tenth day? The patient probably underwent surgical exploration of the neck and had a parathyroid adenoma removed.

Was there a relation between the parathyroid disease and peptic ulcer? Rogers and Keating,[4] in 1947, first called attention to the association of hyperparathyroidism and peptic ulcer and thought the association higher than might be explained by sheer coincidence. According to Howard and his associates[5] at Johns Hopkins 15 per cent of patients with hyperparathyroidism have also had peptic ulcers. Dr. Walter St. Goar,[6] who has reviewed all the cases of hyperparathyroidism in this hospital, found an incidence of 8.8 per cent; almost 50 per cent of these patients had no more ulcer symptoms after the removal of the offending glands. Ten out of 12 had adenomas. Thus, there is some clinical evidence that the two diseases are related. Rutishauser and Majno[7] reported that dogs responded to 100 to 400 units of Para-thor-mone with elevated serum and urinary calcium, lower serum phosphorus, high alkaline phosphatase and also very high levels of blood pepsin. Histologic studies of the gastric mucosas revealed necrosis in the glandular cul-de-sacs of the funduses, with destruction of the chief cells that was accompanied by deposits of calcium salts in these areas. These investigators have suggested that high levels of Para-thor-mone caused lysis of bone, producing hypercalcemia with resultant precipitation of calcium salts in the gastric mucosa around the cells that secrete acid, which are then left relatively alkaline; this phase is followed by necrosis in the glandular cul-de-sac and liberation of pepsinogen contained in these cells that is taken into the blood stream by capillary reabsorption and excreted in the urine as uropepsin. That such a scheme is the explanation of peptic ulcer seen in conjunction with hyperparathyroidism has not been proved but certainly is suggested. Some of the patients in this hospital have had gastric operations before the parathyroid operations. It might be interesting to review the microscopical sections of the gastric mucosa in these cases to see if histologic findings comparable to those described by these investigators can be found. That hyperparathyroidism has an effect on the gastrointestinal tract there can be no doubt. Many of the symptoms are shared in common with peptic ulcer, and prompt relief is usual after removal of the parathyroid tissue. I should expect that this patient's ulcer symptoms diminished after parathyroidectomy. A danger to be kept in mind in cases like this is that of parathyroid poisoning secondary to a high calcium intake. There

was nothing in the protocol to suggest that that occurred in this patient.

DR. WINFIELD S. MORGAN: Dr. Kranes, will you tell us the opinion on the ward?

DR. ALFRED KRANES: The operation mentioned was not, as Dr. Ragland suggested, an exploration of the neck but a subtotal gastric resection. I had come to exactly the same conclusions that Dr. Ragland had — namely, that this patient had an obstructing duodenal ulcer and hyperparathyroidism. Whether I should have handled this situation any differently now than in 1951, when this patient was in the hospital, I have often wondered. At the time, it seemed to me that the main problem confronting us was a nutritional one and that pyloric obstruction was the problem to be solved first. Whether removal of the parathyroid tumor would have improved this situation I frankly do not know. This patient's hypercalcemia did not seem severe enough to account for such striking gastric atony. In any event I decided to have her stomach operated on, and the operation was performed by Dr. Robert R. Linton.

CLINICAL DIAGNOSES

Duodenal ulcer, with pyloric obstruction.
Hyperparathyroidism.

DR. STUART RAGLAND, JR.'S, DIAGNOSES

Adenoma of parathyroid gland.
Primary hyperparathyroidism.
Duodenal ulcer, active, with pyloric obstruction.

ANATOMICAL DIAGNOSES

Duodenal ulcer, active, with pyloric obstruction.
Adenoma, right lower parathyroid gland.

PATHOLOGICAL DISCUSSION

DR. KRANES: At operation Dr. Linton found a very narrow, scarred pylorus. It seems to me highly improbable that correction of the hyperparathyroidism could have improved this situation. The patient recovered quite uneventfully except for a mild dumping syndrome for some months. After her recovery was complete, I tried to induce her to have her neck explored, but she steadily resisted my suggestions. It was at that time that I wished I had reversed the procedure. Once a patient's primary symptom has been relieved it is exceedingly difficult to get him to consent to an operation that does not promise to relieve any immediate symptoms. Nevertheless, I persisted in my attempts and eventually she yielded. Dr. Cope explored the neck about eight months after the gastrectomy.

DR. MORGAN: Dr. Cope, will you describe the operative findings.

DR. OLIVER COPE: At operation the parathyroid gland was promptly encountered on the posterolateral aspect of the right thyroid lobe at the junction of the middle and lower thirds. It appeared to be a large normal gland. No evidence of adenoma was found. The thyroid lobe was freed, but no other parathyroid gland was seen. It was therefore decided to look at the parathyroid gland in the comparable position on the left side. The comparable gland on the left was promptly identified; it was near the network of the inferior thyroid vessels, in a lateral plane, somewhat anterior to the posterior surface of the thyroid gland. This gland, like the one on the right, obtained its blood supply from the surface of the thyroid gland. It was larger than the gland on the right, was brown and gave no gross evidence of either an adenoma or atrophy. We then explored downward, but found no further parathyroid tissue so we explored upward. On the right side a moderately large parathyroid adenoma was identified swinging downward behind the inferior thyroid artery and lateral to the recurrent laryngeal nerve. It lay between the esophagus and the carotid sheath and was not continuous with the thyroid lobe. The adenoma was encapsulated and was easily freed with its capsule intact. It measured 3 by 1.5 by 0.5 cm. An upper parathyroid gland was not found on the left side. The exploration was discontinued because the adenoma was considered adequate to account for the patient's disease.

DR. MORGAN: The first specimen consisted of the distal segment of stomach with attached duodenal cuff. Chiefly in the duodenal portion but also extending onto the pylorus was a typical peptic-ulcer type of deformity associated with considerable fibrosis of the wall and narrowing of the lumen. Microscopical sections through the area of deformity showed a re-epithelialized ulcer crater, with chronic inflammation and scarring but no active peptic ulceration. Permanent sections of the specimen removed by Dr. Cope confirmed the gross and frozen-section diagnosis of parathyroid adenoma.

Dr. Ragland has referred to papers reporting an increased incidence of peptic ulcer in patients with hyperparathyroidism, and he has called attention to the study by Rutishauser and Majno[7] in which animals given Para-thor-mone were found to have calcium deposits in the gastric mucosa. Although the therapy as proposed — attributing the peptic ulceration to the deposition of calcium in the gastric mucosa as a result of the hypercalcemia brought on by the hyperparathyroidism — would be a neat way of explaining the concomitant occurrence of these two conditions, there are certain discrepancies that make me hesitate to accept this as the explanation. Examination of the microscopical sections of the stomach in the case under discussion, as well as those from several other patients with hyperparathyroidism and duodenal ulcer treated by partial gastrectomy in this hospital, does not reveal any calcium deposition. Similarly, in the cases of hyperparathyroidism with a history of peptic ulcer reported by Rogers[8] and Rogers et al.,[4] although

metastatic calcification in the kidneys, heart and lungs was found, there apparently was no calcification of the stomach. On the other hand, of the 21 cases of metastatic calcification reported by Mulligan[9] as occurring in patients with hyperparathyroidism, in most of whom the degree of hyperparathyroidism was very severe, only 6 had metastatic calcification in the stomach. The original articles on 3 of these 6 cases were available, and none mentioned a history of peptic ulcer. It seems to be quite clear from these reports, as well as from our own experience here, that metastatic calcification in the stomach occurs in these cases only when the hyperparathyroidism is severe; yet we find that such cases are not necessarily associated with peptic ulcer. Finally, the patient discussed today, as well as some of the others who had peptic ulcer, did not have severe hyperparathyroidism. These several inconsistencies make me consider it unlikely that the occurrence of peptic ulcers in patients with hyperparathyroidism is due to calcium deposition in the stomach, and I think that some other mechanism is involved.

That peptic ulcers in patients with hyperparathyroidism are significantly frequent seems to be definitely established, and yet the explanation of this facet of hyperparathyroidism may require attention for some time to come. There is still another reference to this combination of findings in a very recent study of 50 patients with hyperparathyroidism by Hellström.[10] Two of 33 women in the series and 5 of 17 men had a history of peptic ulcer, and in all cases the ulcers were duodenal.

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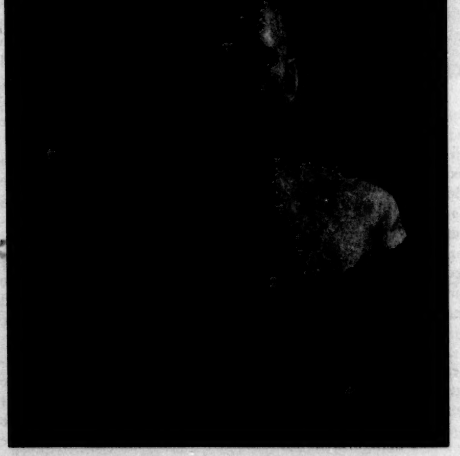

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29. Dr. Franklin G. Balch

Exhibited at Massachusetts Physicians Art Exhibit

Massachusetts, 1952

Sculpture by

Sidney C. Wiggin, M.D.

President, Massachusetts Physicians Art Society

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BOSTON'S NEW DIRECTOR OF HOSPITALS

LATE in June it became common knowledge that John Conlin, director of information and education of the Massachusetts Medical Society, would accept the newly created post of director of hospitals for the City of Boston. This position, entailing the responsibility for an annual budget of over $15,000,000 and the oversight of some 6000 employees, includes the administration of the Boston City Hospital, the Long Island Hospital and the Boston Sanatorium at Mattapan. It is reasonable to suppose that the administrative ability and skill in public relations shown by Dr. Conlin in developing from the ground up the Society's department of information and education was largely responsible for his selection for this new and important office.

John Conlin was born forty-six years ago in Schenectady, New York, the son of a metallurgist at the General Electric Company Laboratory in that city. After graduating from the local public schools he spent nine years studying for the priesthood in various Passionist monasteries; deciding then that medicine rather than theology was his bent he entered Boston College as a premedical student in 1932, taking his degree as a bachelor of arts in 1934. He graduated from Tufts College Medical School in 1938, interned at St. Elizabeth's Hospital in Brighton and served a residency at the John Adams Hospital in Chelsea; in addition to his medical degree he holds those of master of public health *cum laude* from Harvard and master of science in public relations from Boston University.

Dr. Conlin entered the Army as a first lieutenant in May, 1942, and was discharged as a full colonel in November, 1946. Much of this time he served with General Patton's Third Army, largely in support of the 101st Air Borne and Fourth Armored divisions. He was awarded the Bronze Star and five battle stars, participating, among other engagements, in the Battle of the Bulge.

A dynamic program of public relations has been John Conlin's contribution to the progress that the Massachusetts Medical Society has made in the seven years since he was asked to organize this new department. During this period he has become not only a buffer between the Society and a not always friendly press and public; he has been an interpreter of the role that medicine has to play in modern living and a walking information bureau for friend and critic alike.

He has been the Society's spokesman on many matters—on emergency medical coverage plans, on fee splitting and other matters of ethics, and on all that pertains to what is glibly called public relations. He inaugurated the Massachusetts Health Conference and directed the Boston chest x-ray program; he developed the Society's health education activities and, acting for the Committee on Legislation, has represented the Society in many legislative matters pertaining to public health and the practice of medicine.

He has fought the antivivisectionists, various efforts to lower the standards of medical practice and the attempts to curtail the efforts of municipalities in promoting the health of their citizens through the fluoridation of water supplies. He organized and led the Massachusetts Society for Medical Research and the campaign in Massachusetts against compulsory federal health insurance, so-called. Acting under a mandate from the Council he organized the Woman's Auxiliary to the Society.

In the present turn of events the Society must reasonably expect, with no matter how much regret, to defer to the greater needs of the City of Boston. Fortunately, the wheel has not turned so far as to remove John Conlin from this area and from membership in the Society that he has served so well. There is no question that his advice and his service will still be available, under circumstances less exacting to him.

In his new position Dr. Conlin will bring his unusual aptitudes and his wide experience to bear on familiar problems from a new vantage point. For his opportunities will far transcend mere administrative duties, important as these may be. It will be his concern to develop and guide a high type of hospital and professional relations to the ultimate benefit of the patient. It will be his mission to help maintain within the institutions under his jurisdiction a teaching organization in which the city of Boston and the three participating medical schools may take mutual pride.

BEAUMONT MEMORIAL

THE story of William Beaumont and his fistulous patient, Alexis St. Martin, is a classic in American medical history. It is a classic, moreover, in the annals of physiologic research — the result of a fortuitous circumstance that made a meagerly trained but resourceful and intelligent frontier army physician a pioneer in clinical investigation. Beaumont and St. Martin are again in the news at this particular time because on July 17 there was dedicated on Mackinac Island, in upper Michigan, a newly completed memorial to Beaumont and the incident that determined his place in history; plans for the memorial had been put on foot in 1952, just prior to the hundredth anniversary of Beaumont's death in 1853.

Beaumont was born at Lebanon, Connecticut, on November 21, 1785; he had left his home at the age of twenty-one to seek his fortune "with a horse and cutter, a barrel of cider, and $100." On his way to Champlain, New York, where he was to teach school for three years, he made the acquaintance of Dr. John Pomeroy, of Burlington, from whom he borrowed books on medicine. Determined on medicine as a career he apprenticed himself in 1810 to Dr. Benjamin Chandler, of St. Albans, Vermont, and two years later was granted his license to practice. In September of that year he joined the army as a surgeon's mate and participated in a number of engagements. In 1815 he entered private practice at Plattsburg, New York, where he remained for nearly four years, re-entering the army as post surgeon early in 1820. His first post was at Mackinac Island, which, two years later, was to become the scene of his most important adventure and his entry into the ranks of science.

The famous incident occurred on June 6, 1822, in the American Fur Company store, when the eighteen-year-old French Canadian *voyageur*, St. Martin, received in the abdomen the full accidental discharge of a shotgun. The story of Beaumont's surgical care of the patient and his subsequent studies of the physiology of digestion by way of St. Martin's gastric fistula is familiar to the most casual student of medical history.

The memorial so recently dedicated is a gift to the people of Michigan from the medical profession of the state through the individual contributions of physicians. It consists of a reconstruction of the original American Fur Company store on the original site and

on the original foundation, adjacent to old Fort Michilimackinac. The stone-walled French habitant-type cottage contains two main rooms of which the larger is the Beaumont Memorial Room, containing Dean Cornwell's well known painting of Beaumont ministering to his patient, Keller's portrait of Beaumont and other objects of historic interest. The smaller room has been stocked with the type of material carried by a similar store of the period.

LUNATIC FRINGE

In May the Interstate and Foreign Commerce Committee of the House of Representatives held hearings on H.R. 2341, "A Bill to protect the public health from the dangers of fluorination of water"; to date the committee has taken no action. No matter how much pressure is brought to bear by faddists, sincere dissentients, publicity seekers, religious zealots, crackpots and the merely uninformed, it remains obvious that "the results of research are not determined in congressional halls but in the laboratories and field studies of the scientist."[1] The proposed bill, which was introduced by Mr. Wier (R), of Minnesota, is as follows:

A BILL

To protect the public health from the dangers of fluorination of water.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That no agency of the Government of the United States (including the government of the District of Columbia, and of each Territory and possession of the United States), and no agency of any State, or of any municipality or other political subdivision of a State, shall treat any public water supply with any fluoride compound, or make any water so treated available for general use in any hospital, post office, military installation, or other installation or institution owned or operated by or on behalf of any such agency.

Scientific knowledge about water fluoridation having been summarized in the *Journal* in 1952[2] and recently in the Report of the Committee of the St. Louis Medical Society[3] and elsewhere, its value need not be set forth here; the evidence is lengthy, and the scientific caliber of the pioneers who have led the way is impressive. The case of the proponents of this bill rests on the charge "that fluorine is a 'highly toxic element.'" Since this unqualified statement is true the implication is given that concentrations of the element advocated in the fluoridation of water are also highly toxic. The same misinformed persons might just as logically introduce another bill to prohibit the consumption of lobsters because iodine, to be found in sea food, is also a "highly toxic element."

It would indeed be a travesty of public health if the constructive steps already taken to promote sound teeth in the communities that have adopted fluoridation as a principle should be sabotaged by passage of H.R. 2341. Artfully disguised as a bill "to protect the public health from the dangers of fluorination" the very title begs the question doubly: once by introducing the phrase implying that danger is demonstrated and again by the intimation that the protagonists of the bill know what public health is and are, presumably, men of standing in that field.

The whole proposal is an action designed to hoodwink the American people into accepting national legislation that favors the lunatic fringe at the expense of those who are scientifically oriented and believe in science as it is practiced by American physicians. It is hardly to be expected that Congress will interfere with the rights of states, cities and towns to protect the health of their citizens.

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DR. LITTLE ISSUES STATEMENT

Dr. Clarence Cook Little, recently appointed scientific director of the Tobacco Industry Research Committee, issued in June a statement regarding the preliminary findings of the five-year survey being conducted by the American Cancer Society.

In noting that Dr. Charles S. Cameron, medical and scientific director of the American Cancer Society, "is not convinced that the Hammond-Horn theory of cause and effect relationship between heavy cigarette smoking and increased susceptibility to death from cancer is as yet entirely proved," Dr. Little also evinces the greatest respect for Drs. Hammond and Horn and confidence "that when their completed data are published, they will be of vital interest to scientists."

Dr. Little, in the concluding paragraphs of his statement, declared that:

> The origin, nature, and development of cancer and of cardiovascular disease are complex problems, offering the greatest existing challenge to creative scientific thought and to further experimentation wisely conceived, patiently executed, and fearlessly and impartially interpreted in our search for the truth.
>
> The Tobacco Industry Research Committee has unqualifiedly given to its Board of scientific advisors and to the present Director of Research complete freedom of thought and action. This freedom will be jealously guarded by the industry and by the scientists concerned in the hope and belief that human welfare can thus be best and most rapidly advanced.

Disgusting Medical Advertisements. — *A society has been formed in London and Manchester, called "the Union for Discouragement of Vicious Advertisements," which by the circulation of tracts calls upon the public to set their faces against papers admitting such advertisements as "Manhood," "The Silent Friend," "Nervous Debility," &c.*—Nottingham Journal.

Boston M. & S. J., *July 26, 1854*